

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



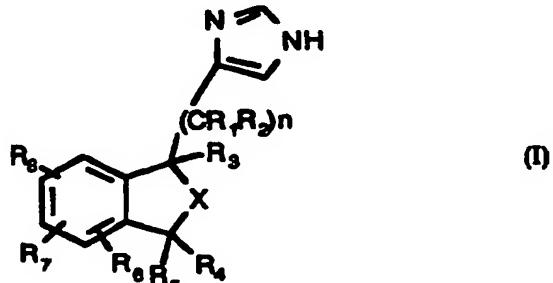
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 233/54, A61K 31/415	A1	(11) International Publication Number: WO 97/12874 (43) International Publication Date: 10 April 1997 (10.04.97)
(21) International Application Number: PCT/FI96/00518		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 2 October 1996 (02.10.96)		
(30) Priority Data: 9520150.5 3 October 1995 (03.10.95) GB		
(71) Applicant (<i>for all designated States except US</i>): ORION-YHTYMA OY [FI/FI]; Orionintie 1, FIN-02200 Espoo (FI).		
(72) Inventors; and		Published
(75) Inventors/Applicants (<i>for US only</i>): KARJALAINEN, Arto [FI/FI]; Myllyojantie 13 H 37, FIN-90650 Oulu (FI). HUHTALA, Paavo [FI/FI]; Hinttatie 23 A 2, FIN-90500 Oulu (FI). SAVOLA, Juha-Matti [FI/FI]; Siutlankatu 8, FIN-20380 Turku (FI). WURSTER, Siegfried [DE/FI]; Uudenmaantie 70 A 19, FIN-20720 Turku (FI). ELORANTA, Maire [FI/FI]; Mäntyrinne 18, FIN-90230 Oulu (FI). SAVOLA, Maarit [FI/FI]; Lahnnatie 9 A 3, FIN-20760 Piispanristi (FI). SAXLUND, Raimo [FI/FI]; Saukkotie 5, FIN-90530 Oulu (FI). COCKCROFT, Victor [GB/FI]; Yliopistonkatu 5 A 9, FIN-20110 Turku (FI). KARJALAINEN, Arja [FI/FI]; Tii-litie 15 C 24, FIN-90650 Oulu (FI).	<i>With international search report.</i>	
(74) Agent: ORION CORPORATION; Orion Pharma, Patent Service, P.O. Box 65, FIN-02101 Espoo (FI).		

(54) Title: IMIDAZOLE DERIVATIVES HAVING AFFINITY FOR ALPHA2 RECEPTORS ACTIVITY

(57) Abstract

Imidazole derivatives of formula (I), wherein n is 0 or 1, R₁ is hydrogen or C₁-C₄-alkyl, R₂ is hydrogen or R₂ and R₃ together form a double bond, R₃ is hydrogen or C₁-C₄-alkyl or R₂ and R₃ together form a double bond, R₄ is hydrogen, C₁-C₄-alkyl, hydroxy or C₁-C₄-alkoxy, R₅ is hydrogen or C₁-C₄-alkyl or R₄ and R₅ together with the carbon atom to which they are attached form a carbonyl group, R₆, R₇ and R₈ are each the same or different and are independently hydrogen, C₁-C₄-alkyl or C₂-C₄-alkenyl, C₃-C₇-cycloalkyl, hydroxy, C₁-C₄-alkoxy, C₁-C₄-hydroxyalkyl, thiol, C₁-C₄-alkylthio, C₁-C₄-alkylthiol, halogen, trifluoromethyl, nitro or optionally substituted amino, X is -CHR₉-(CHR₁₀)_m, m is 0 or 1, and R₉ and R₁₀ are each the same or different and are independently hydrogen or C₁-C₄-alkyl; or a pharmaceutically acceptable ester or salt thereof, their preparation, use and pharmaceutical compositions comprising them are described. The compounds have affinity for alpha2 receptors and are useful e.g. in the treatment of hypertension, glaucoma, chronic or acute pain, migraine, diarrhea, common cold, ischemia, addiction to chemical substances, anxiety, especially preoperative anxiety and different neurological, musculoskeletal, psychiatric and cognition disorders or as adjuncts to anesthesia.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

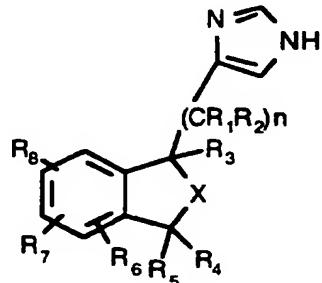
IMIDAZOLE DERIVATIVES HAVING AFFINITY FOR ALPHA2 RECEPTORS ACTIVITY

The present invention relates to substituted 4(5)-(1-indanyl and 1-indanylmethyl and 1-indanylmethylen)imidazoles and 4(5)-[1-(1,2,3,4-tetrahydronaphthyl and 1,2,3,4-tetrahydronaphthylmethyl and 1,2,3,4-tetrahydronaphthylmethylen]imidazoles and to their isomers, pharmaceutically acceptable salts and esters. It also relates to their preparation, use and to pharmaceutical compositions containing them.

The compounds of the invention have affinity for alpha2 receptors most of them being very selective alpha2 agonists. Accordingly, they are useful in the treatment of hypertension, glaucoma, migraine, diarrhea, ischemia, addiction to chemical substances (such as tobacco and narcotics) and different neurological, musculoskeletal, psychiatric and cognition disorders as well as sedative and analgesic agents, nasal decongestants, and adjuncts to anaesthesia.

Gregory G. B., et al describe in J. Org. Chem. (1990), 55, 1479-1483 a new synthesis step for 1-phenylalkyl-1-(4-imidazolyl)-1,2,3,4-tetrahydronaphthalene derivatives which are useful as nonpeptide antagonists of the angiotensin II receptor.

The imidazole derivatives of the invention are either compounds of formula I



n is 0 or 1

R1 is hydrogen or C1-C4-alkyl

R2 is hydrogen or R2 and R3 together form a double bond

R3 is hydrogen or C1-C4-alkyl or R2 and R3 together form a double bond

R4 is hydrogen, C1-C4-alkyl, hydroxy or C1-C4-alkoxy

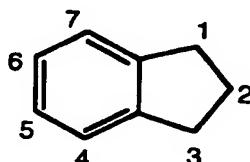
R5 is hydrogen or C1-C4-alkyl or R4 and R5 together with the carbon atom to

- which they are attached form a carbonyl group
- R₆, R₇ and R₈ are each the same or different and are independently hydrogen, C₁-C₄-alkyl or C₂-C₄-alkenyl, C₃-C₇-cycloalkyl, hydroxy, C₁-C₄-alkoxy, C₁-C₄-hydroxyalkyl, thiol, C₁-4-alkylthio, C₁-4-alkylthiol, halogen, trifluoromethyl, nitro or optionally substituted amino
- X is -CHR₁₀-(CHR₁₁)_m-
- m is 0 or 1
- and R₉ and R₁₀ are each the same or different and are independently hydrogen or C₁-C₄-alkyl;
- 10 or a pharmaceutically acceptable ester or salt thereof.

The terms as employed herein have the following meanings:

- A halogen is e.g. chlorine, bromine or fluorine, preferably it is chlorine or fluorine. The C₁-C₄-alkyl, C₁-C₄-alkoxy and C₂-C₄-alkenyl etc. groups may be branched or straight chain groups. C₃-C₇-Cycloalkyl is a saturated cyclic hydrocarbon group having preferably 3 to 5 carbon atoms. Optionally substituted amino is an amino group which is unsubstituted or substituted with a C₁-C₄-alkyl group.

When m=n=0



20

- R₃ is preferably hydrogen,
- R₄ is preferably hydrogen, hydroxy or C₁-C₄-alkoxy, such as ethoxy,
- R₅ is preferably hydrogen, or R₄ and R₅ form, together with the carbon atom to which they are attached, a carbonyl group.
- 25 R₆ is preferably hydrogen, C₁-C₄-alkyl, such as methyl, ethyl, t-butyl, hydroxy or C₁-C₄-alkoxy, such as methoxy. For example, R₆ may be C₁-C₄-alkyl at position 4, 5 or 6, such as 4-methyl, 4-t-butyl, 5-methyl, 6-methyl, 6-ethyl, 6-t-butyl, 6-i-butyl, hydroxy at position 5 or position 7, or a C₁-C₄-alkoxy at position 5, 6 or 7, such as 5-, 6- or 7-methoxy.
- 30 More preferably R₆ is hydrogen, 4-methyl, 6-methyl or 7-methoxy.
- R₇ is preferably hydrogen, C₁-C₄-alkyl, such as, for example methyl or t-butyl, hydroxy or C₁-C₄-alkoxy, for example methoxy. For example R₇ may be a C₁-C₄-alkyl at position 5, 6 or 7, such as 5-methyl, 7-methyl, 6-t-butyl, 7-hydroxy

or 7-methoxy.

More preferably R₇ is hydrogen.

R₈ is preferably hydrogen, hydroxy or C₁-C₄-alkoxy, such as methoxy. For example, R₈ may be 6-hydroxy or 7-hydroxy, a C₁-C₄-alkoxy at position 6,

5 such as 6-methoxy.

R₉ is preferably hydrogen or methyl.

When n=1 and m=0

R₁ is preferably hydrogen, methyl or ethyl.

10 R₂, R₃ and R₉ are preferably hydrogen.

R₄ and R₅ are preferably hydrogen or methyl.

R₆ is preferably hydrogen, C₁-C₄-alkyl, such as methyl or t-butyl, hydroxy, C₁-C₄-alkoxy, such as methoxy or C₁-C₄-hydroxyalkyl, such as hydroxymethyl or halogen. For example, R₆ may be a C₁-C₄-alkyl at position 4 or 5, such as 4-
15 or 5-methyl or 4- or 5-t-butyl, 4-, 5-, 6- or 7-hydroxy, a C₁-C₄-alkoxy at position 5, 6 or 7 such as 5-, 6- or 7-methoxy or C₁-C₄-hydroxyalkyl at position 5 such as 5-hydroxymethyl. R₆ may be halogen at position 5 or 6, such as 5- or 6-fluoro or 5- or 6-bromo.

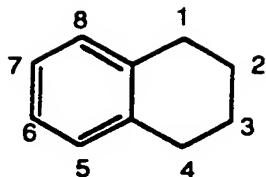
More preferably R₆ is 4-, 5- or 6-hydroxy.

20 R₇ is preferably hydrogen, C₁-C₄-alkyl, hydroxy, C₁-C₄-alkoxy, C₁-C₄-hydroxyalkyl or halogen. For example, R₇ may be C₁-C₄-alkyl at position 5, 6 or 7, such as 5- or 7-methyl or 5- or 6-t-butyl, 5- or 6-hydroxy, or C₁-C₄-alkoxy at position 6, such as 6-methoxy, C₁-C₄-hydroxyalkyl at position 6, such as 6-hydroxymethyl or halogen at position 5, such as 5-bromo.

25 More preferably R₇ is hydrogen, 6-t-butyl, 6-hydroxy or 6-hydroxymethyl.

R₈ is preferably hydrogen, C₁-C₄-alkyl, hydroxy, C₁-C₄-alkoxy or halogen, for example C₁-C₄-alkyl at position 7, such as 7-methyl or 7-t-butyl, 6- or 7-hydroxy or C₁-C₄-alkoxy at position 6, such as 6-methoxy or halogen at position 7 such as 7-bromo.

30 Especially preferably R₆ is hydroxy at the position 4 or 6 of the indane ring and R₇ and R₈ are hydrogen or R₆ is hydroxy at the position 5 of the indane ring and R₇ is hydroxy or C₁-C₄-alkyl or C₁-C₄-hydroxyalkyl at the position 6 of the indane ring, such as 6-t-butyl or 6-hydroxymethyl and R₈ is hydrogen.

When n=m=1

- R₁, R₂, R₃, R₅, R₉ and R₁₀ are preferably hydrogen.
- 5 R₄ is preferably hydrogen or C₁-C₄-alkyl, such as, for example, methyl.
R₆ is preferably at position 5, 6 or 7.
R₆ is preferably hydrogen, hydroxy, C₁-C₄-alkoxy, for example methoxy, or halogen. For example, R₆ may be 5-, 6- or 7-methoxy, 6- or 7-hydroxy or halogen at position 6, such as 6-bromo.
- 10 R₇ is preferably at position 7.
R₇ is preferably hydrogen or C₁-C₄-alkyl, such as, for example, 7-t-butyl or 7-hydroxy.
R₈ is preferably at position 8.
R₈ is preferably hydrogen or halogen such as 8-bromo.

15

When n=0 and m=1

R₃, R₄, R₅, R₇, R₈, R₉ and R₁₀ are preferably hydrogen.

R₆ is preferably hydrogen or halogen, for example chlorine. R₆ may be a halogen at position 5, such as, for example 5-chloro.

- 20 The invention includes within its scope all the possible isomers and stereoisomers, in particular Z and E (cis and trans isomers) and enantiomers.

- 25 The compounds of the formula (I) form acid addition salts with both organic and inorganic acids. Typical acid addition salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates. Furthermore, compounds wherein one or more of R₄ to R₈ is a hydroxy group form esters and salts with alkali metals and alkaline earth metals. Typical esters include the lower alkyl esters, such as the methyl, ethyl and propyl esters.

- 30 The compounds of the invention may be prepared using the following methods. (It is to be noted that in the formulae below, when the imidazole

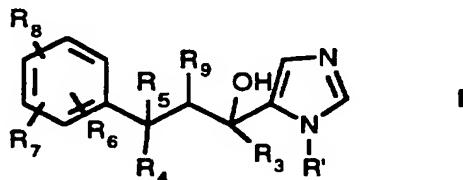
group is protected, the protecting group R' (benzyl or trityl) may be attached to either of the two nitrogen atoms of the imidazole ring. Accordingly, the use of 1-benzyl-5-imidazolecarbaldehyde as starting material leads to 1.5 substituted derivatives whereas when trityl is used the substitution is mainly 1.4.)

5 Synthesis of 4(5)-(1-indanyl)imidazoles and the corresponding 4(5)-[1-(1,2,3,4-tetrahydronaphthyl)]imidazoles

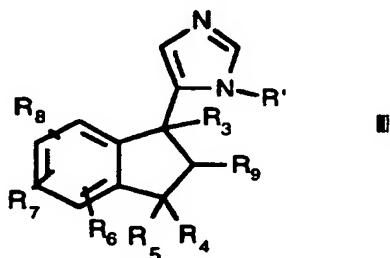
Method a

Compounds of formula I wherein n=0 and m=0 or 1 may be prepared by an acid catalyzed cyclization of protected or unprotected 4(5)-(1-hydroxy-3-phenylpropyl or 1-hydroxy-4-phenylbutyl)imidazoles of formulae II and II', respectively.

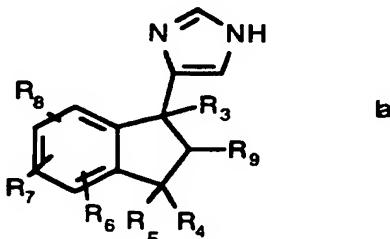
Accordingly, the 4(5)-(1-indanyl)imidazoles may be prepared by cyclization of the compound of formula II



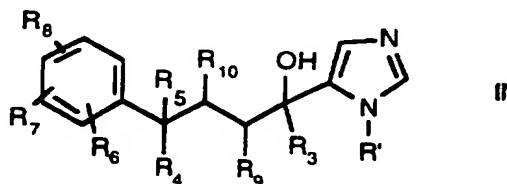
15 wherein R₃ to R₉ are as defined above and R' is a protecting group, in the presence of an acid to form the compounds of formula III



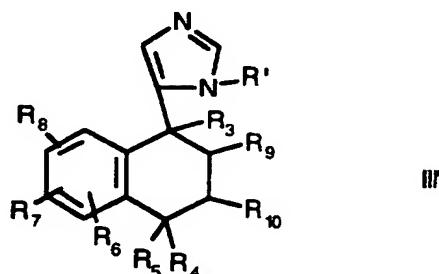
wherein the substituents are as defined above, and removing the protecting group R' to form the compounds of formula Ia



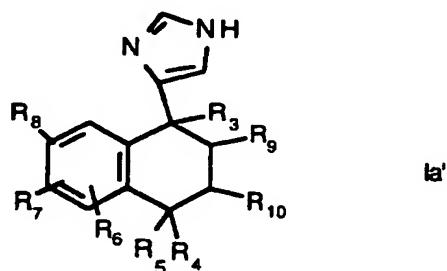
The corresponding 4(5)-[1-(1,2,3,4-tetrahydronaphthyl)]imidazoles may be prepared by cyclization of the compound of II'



5 wherein R₃ to R₁₀ are as defined above I and R' is a protecting group in the presence of an acid to form the compounds of formula III'



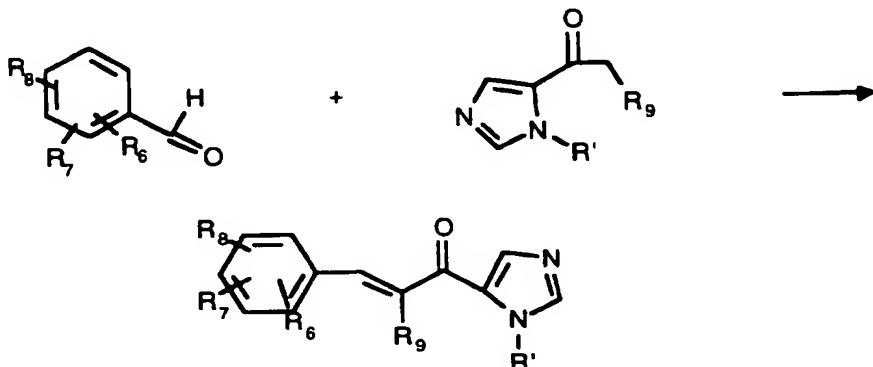
wherein the substituents are as defined above, and removing the protecting group R' to form the compounds of formula Ia'



10 wherein the substituents are as defined above.

The protecting group R' may be, for example, benzyl or trityl. When R' is trityl it may be removed using an acid and, when it is benzyl, by catalytic hydrogenation. The acid used in the cyclization reaction may be, for example, polyphosphoric acid (PPA) or methanesulfonic acid.

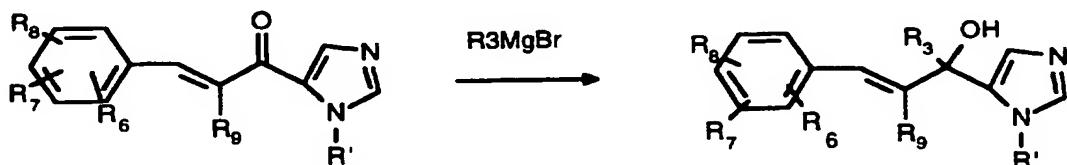
15 The starting materials (compounds of the formulae II and II', respectively) may be synthesized using different methods. One of them is to prepare α,β-unsaturated ketones through an aldol condensation by allowing an imidazolyl alkyl ketone to react with an appropriately substituted benzaldehyde in the presence of a base:



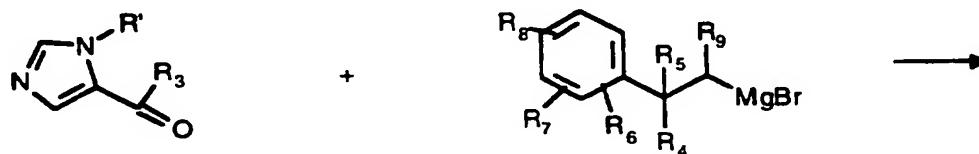
The accompanying reduction of carbonyl and the following catalytic hydrogenation produces saturated alcohols used in the cyclization. The reduction of the carbonyl group may be performed for example with sodium borohydride. If the imidazole moiety has been substituted with the benzyl group it may also be removed by catalytic hydrogenation.

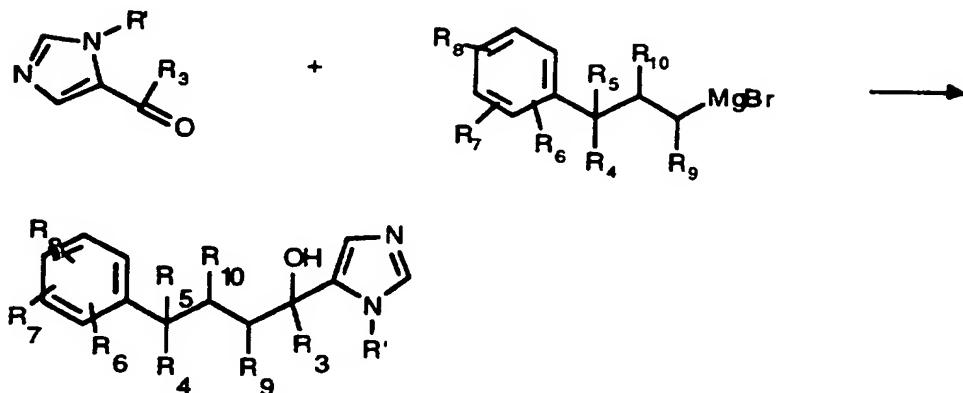
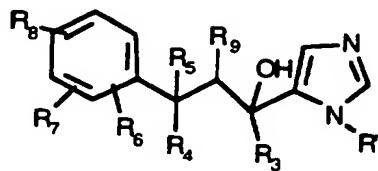
To accomplish substitution at the position 1 of the indane or 1,2,3,4-tetrahydronaphthalene ring it is possible to carry out an 1,2-addition reaction of the intermediate ketone with a nucleophile before the hydrogenation. This is conveniently performed through the Grignard reaction which is carried out by adding to the reaction mixture an alkyl magnesium halide, e.g. bromide, made from alkyl halide and magnesium:

15



Another useful method to produce appropriate alcohols needed as starting materials in the cyclization is the use of the Grignard reaction in the preparation of 4(5)-(1-hydroxy-phenylalkyl)imidazoles. Here the 4(5)-imidazole carbaldehyde or ketone is allowed to react with a Grignard reagent, prepared from appropriately substituted phenylalkyl halide and magnesium:



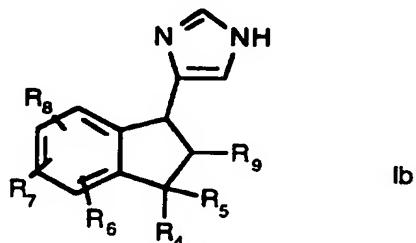


5

Method b

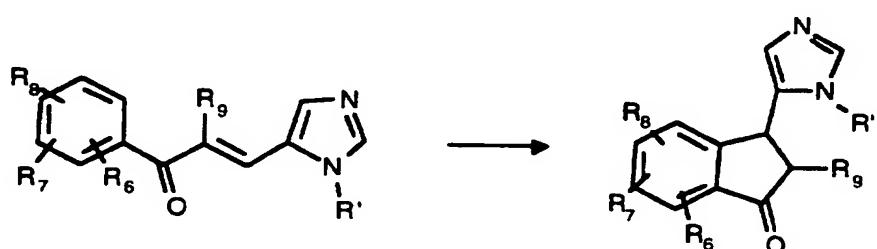
To obtain substitution at the position 3 of the indane group the following procedure may be used: An intermediate of formula Ib, which is also an active compound wherein R4 and R5 together form a carbonyl group, is prepared.

10



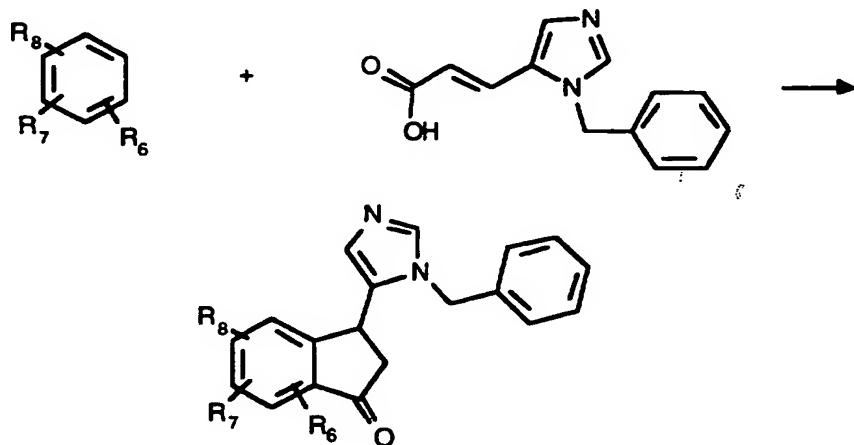
There are different methods for the preparation of this intermediate.

Firstly, it may be prepared using an acid catalyzed cyclization of 1-aryl-3-[4(5)-imidazolyl]- α,β -unsaturated-1-propanones:



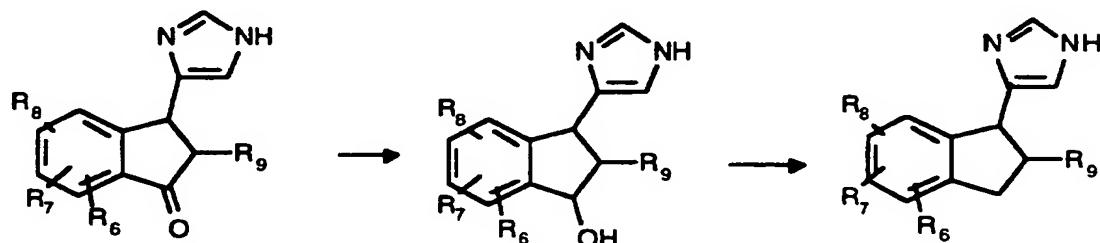
The α,β -unsaturated ketone used as the starting material in the above reaction may be prepared by a base catalyzed aldol condensation from substituted or unsubstituted 4(5)-imidazole carbaldehyde and from appropriately substituted phenyl alkyl ketone.

- 5 Secondly, it may be prepared through the condensation of benzyl protected urocanic acid with an appropriately substituted benzene:



- 10 The benzyl protection is abolished by hydrogenation as described earlier.

The ketone group may be then further modified using different methods. It may be reduced to the corresponding alcohol with sodium borohydride or by catalytic hydrogenation, whereafter the alcohol may be hydrogenated:



15

It is also possible to modify the ketone group using Grignard reaction:

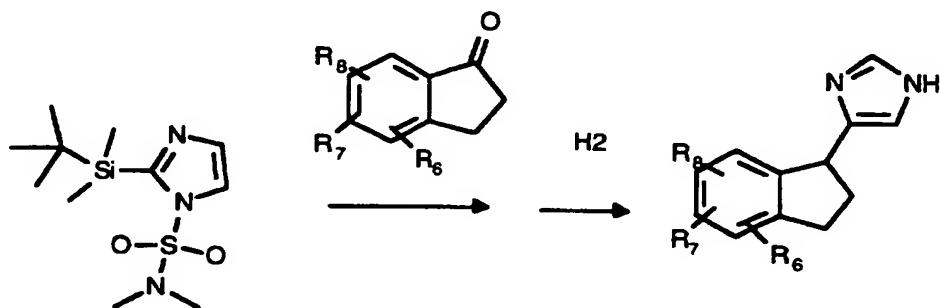


These compounds may be further transformed to compounds of formula I wherein n=m=0 and R₄ is an alkyl and R₅ is hydrogen by catalytic hydrogenation as described above.

- 5 The compounds of formula Ib wherein R₄ is alkoxy and R₅ is hydrogen may be prepared from the corresponding alcohol in concentrated hydrochloric acid.

Method c

- A further method to synthesize the 4(5)-(1-indanyl)imidazoles of the
 10 formula I is to use the lithiated imidazole in an aromatic electrophilic substitution reaction with an 1-indanone (imidazole being bis-protected according to the method described by Kudzma et al. in *Synthesis*, (1991), p. 1021). The protection may be removed by acid treatment, which induces the simultaneous loss of water. The double bond is reduced by catalytic
 15 hydrogenation as described above.



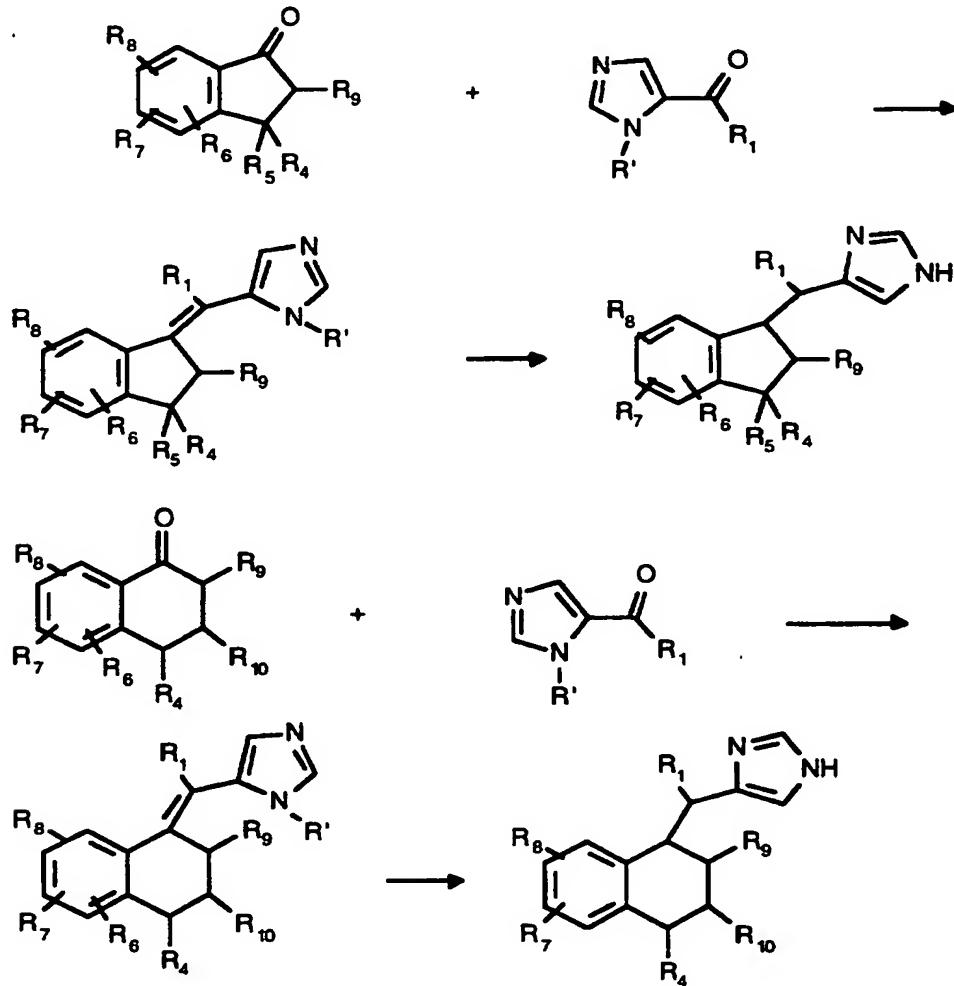
Synthesis of 4(5)-(indan-1-ylmethyl)imidazoles and 4(5)-(indan-1-ylmethylen)imidazoles and the corresponding tetrahydronaphthyl derivatives

- 20 Method d

The preparation of 4(5)-(indan-1-ylmethyl and indan-1-ylmethylen)imidazole and the corresponding tetrahydronaphthyl skeleton may

be accomplished using the so called McMurry reaction, in which an imidazole carbaldehyde or ketone reacts with an 1-indanone. The reaction is catalyzed by low valence titanium. The condensation may be followed by the hydrogenation of the double bond and simultaneous elimination of the protecting group in the imidazole ring.

5



10

The compounds of the invention may be administered enterally, topically or parenterally. Parenteral administration is used, for example, when the compounds are given as sedative or anxiolytic agents in connection to different clinical operations and to cause analgesia or to potentiate anesthesia.

15

The compounds of the invention may be formulated alone or together with another active ingredient and / or a pharmaceutically acceptable diluent or carrier to different pharmaceutical unit dosage forms i.e. tablets, capsules, solutions, emulsions and powders etc. using conventional techniques. The

pharmaceutical carriers employed are selected with the planned manner of administration in mind. Thus, solid carriers may include lactose, sucrose, gelatin and agar, while liquid carriers typically include water, syrup, peanut oil and olive oil. The amount of the active ingredient varies from 0.01 to 75 weight-% depending on the type of the dosage form.

The appropriate oral dosage for the compounds of the invention depends on several factors such as the compound to be administrated, the species, age and the sex of the subject to be treated, the condition to be treated and on the method of administration. Accordingly, the dosage for parenteral administration is typically from 0.5 µg/kg to 10 mg/kg per day and that for oral administration is from 5 µg/kg to 100 mg/kg for an adult male.

The invention also provides a compound of the invention or an ester or salt thereof for use in a method of treatment of human or animal body.

The present invention further provides a compound of the invention or an ester or salt thereof for use in the treatment of hypertension, glaucoma, chronic and acute pain, migraine, diarrhea, common cold, ischemia, addiction to chemical substances, anxiety, especially preoperative anxiety and different neurological, musculoskeletal, psychiatric and cognition disorders or as an adjunct to anesthesia.

The invention also provides the use of a compound of the invention or an ester or salt thereof in the manufacture of a medicament for the treatment of hypertension, glaucoma, chronic and acute pain, migraine, diarrhea, common cold, ischemia, addiction to chemical substances, anxiety, especially preoperative anxiety and different neurological, musculoskeletal, psychiatric and cognition disorders or as an adjunct to anesthesia.

The invention further relates to a method for the treatment of hypertension, glaucoma, chronic and acute pain, migraine, diarrhea, common cold, ischemia, addiction to chemical substances, anxiety, especially preoperative anxiety and different neurological, musculoskeletal, psychiatric and cognition disorders by administering to a subject in need of such treatment an effective amount of the compound of the invention or a pharmaceutically acceptable ester or salt thereof.

Test results

1. Alpha2 agonism in rat vas deferens model

5 Alpha2 agonism was determined by means of isolated, electrically stimulated prostatic portions of rat vas deferens preparation (Virtanen et al. Arch. Int. Pharmacodyn et Ther. 297 (1989), pp. 190-204). In this model, an alpha2 agonist is able to inhibit electrically induced muscular contractions by activating the presynaptic alpha2 adrenoceptors and thus diminishing the
10 secretion on the motor transmitter. The known alpha2 agonist dexmedetomidine was used as reference substance. Results are shown in Table 1, where the alpha2 agonist effect is presented as the pD₂-value (negative logarithm of the molar concentration of the compound producing 50 percent of maximal inhibition).

15 The following compounds were tested:

- 1 4-(4-Methylindan-1-yl)-1H-imidazole hydrochloride
- 2 3-(1H-Imidazol-4-ylmethyl)-indan-5-ol hydrochloride
- 3 4-[1-(Indan-1-yl)-ethyl]-1H-imidazole hydrochloride
- 4 8-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydronaphthalen-2-ol hydrochloride
- 20 5 dexmedetomidine (reference compound)

Table 1 Alpha2 agonism in vitro

Compound	pD ₂ -value
1	8.1+-0.2
2	8.5+-0.1
3	8.9+-0.3
4	7.0+-0.1
5	8.4+-0.1

2. Binding assays

Affinities for α_2 -adrenoceptors and α_1 -adrenoceptors were estimated by determining the displacement of 1 nM ^3H -RX821002 (α_2) or 0.1 nM ^3H -prazosin (α_1) from α -adrenoceptors in rat neocortical membranes. For this purpose membranes were incubated with different concentrations of test compounds spanning a concentration range of five orders of magnitude. Nonspecific binding was defined with 10 μM phentolamine. Membranes were used at a protein concentration of 2 mg/ml in a total volume of 250 μl . The 10 incubation buffer consisted of 50 mM TRIS-HCl, pH 7.7. After a 30 min incubation at 25 °C samples were filtered through glass fibre filter and filters were washed three times with 4 ml icecold wash buffer consisting of 10 mM TRIS-HCl, pH 7.7. Filters were then dried, impregnated with a scintillation cocktail and counted in a scintillation counter. Experimental data was 15 analyzed using the commercial nonlinear least squares computer program LIGAND.

Each compound was tested in at least three independent experiments for its affinity on rat neocortical α_2 - or α_1 -adrenoceptors. The results are shown in Table 2.

20

Table 2 Affinity on rat neocortical α_2 - or α_1 -adrenoceptors

Compound	pKi α_2	pKi α_1	alpha2 vs alpha1 selectivity
1	8.44	7.31	14
2	8.70	6.61	126
3	8.35	6.21	142
4	7.39	6.85	3
5	8.42	6.48	90

The following examples illustrate how compounds of the invention may be prepared.

EXAMPLE 1

5

4-(6-tert-Butylindan-1-yl)-1H-imidazole

a) 3-(4-tert-Butylphenyl)-1-(1H-imidazol-4-yl)-propan-1-ol

10 A solution of 4-tert-butylbenzaldehyde (5.7 g), 1-(3-benzyl-3H-imidazol-4-yl)-ethanone (7.0 g) and 48 % sodium hydroxide (2.0 ml) in methanol (60 ml) is heated at 60-65 °C for 11 hours. The reaction mixture is then cooled in an ice bath. The resulting precipitate is filtered and the solid intermediate 1-(3-benzyl-3H-imidazol-4-yl)-3-(4-tert-butylphenyl)-propen-1-one is rinsed with 15 methanol. The yield is 10.0 g.

20 The intermediate is dissolved in the mixture of ethanol (170 ml) and concentrated hydrochloric acid (3 ml). The reaction mixture is hydrogenated at 50-60 °C with 10 % palladium on carbon as catalyst until no more hydrogen is consumed. The mixture is filtered and the filtrate is evaporated to dryness. The residue is dissolved in water and is made alkaline with sodium hydroxide. The product is then extracted into methylene chloride which is washed with water, dried with sodium sulfate and evaporated to dryness. The product is converted to its hydrochloride salt in ethyl acetate using dry hydrochloric acid. The yield is 6.8 g.

25 ^1H NMR (as HCl-salt, MeOH-d₄): 1.29 (s, 9H), 2.06-2.13 (m, 2H), 2.62-2.78 (m, 2H), 4.77 (t, 1H), 7.13 (m, 2H), 7.30 (m, 2H), 7.40 (s, 1H), 8.79 (s, 1H)

b) 4-(6-tert-Butylindan-1-yl)-1H-imidazole

30 A mixture of 3-(4-tert-butylphenyl)-1-(1H-imidazol-4-yl)-propan-1-ol (2.0 g) and methanesulfonic acid (30 ml) is heated at 60 °C for 5 minutes. The reaction is then quenched by pouring it into ice-water solution. The acidic solution is made basic with ammonium hydroxide solution, and extracted with ethyl acetate. The combined organic layers are washed with water, dried 35 with sodium sulfate, and evaporated to dryness under reduced pressure. The crude product is purified by flash chromatography by eluting with methylene

chloride -methanol as eluent. The product is crystallized from ethyl acetate. The yield is 220 mg.

5 ¹H NMR (MeOH-d₄): 1.24 (s, 9H), 2.07-2.20 (m, 1H), 2.43-2.54 (m, 1H), 2.81-3.01 (m, 2H), 4.35 (t, 1H), 6.74 (s, 1H), 7.09 (s, 1H), 7.14-7.21 (m, 2H), 7.60 (s, 1H)

Using the same method the following compounds were prepared:

4-(Indan-1-yl)-1H-imidazole

10 ¹H NMR (CDCl₃): 2.08-2.19 (m, 1H), 2.41-2.51 (m, 1H), 2.80-2.95 (m, 2H), 4.37 (t, 1H), 6.65 (s, 1H), 7.07-7.21 (m, 4H); 7.25 (s, 1H)

4-(4-Methylindan-1-yl)-1H-imidazole. M.p. of hydrochloride 153-156 °C

15 ¹H NMR (as HCl-salt, MeOH-d₄): 2.08-2.20 (m, 1H), 2.30 (s, 3H), 2.58-2.69 (m, 1H), 2.87-3.10 (m, 2H), 4.59 (t, 1H), 6.89 (d, J=7.0 Hz, 1H), 7.05-7.13 (m, 2H), 7.30 (s, 1H), 8.83 (s, 1H)

4-(6-Methylindan-1-yl)-1H-imidazole

20 ¹H NMR (as HCl-salt, MeOH-d₄): 2.07-2.20 (m, 1H), 2.28 (s, 3H), 2.55-2.66 (m, 1H), 2.89-3.08 (m, 2H), 4.53 (t, 1H), 6.88 (s, 1H), 7.06 (d, J=7.8 Hz, 1H), 7.19 (d, J=7.8 Hz, 1H), 7.30 (s, 1H), 8.79 (s, 1H)

4-(6-Ethylindan-1-yl)-1H-imidazole

25 ¹H NMR (as HCl-salt, MeOH-d₄): 1.17 (t, 3H), 2.08-2.21 (m, 1H), 2.55-2.67 (m, 3H), 2.90-3.10 (m, 2H), 4.56 (t, 1H), 6.91 (s, 1H), 7.08 (d, J=7.7 Hz, 1H), 7.22 (d, J=7.7 Hz, 1H), 7.32 (s, 1H), 8.85 (s, 1H)

4-(4,5-Dimethylindan-1-yl)-1H-imidazole. M.p. of hydrochloride 161-164 °C.

30 ¹H NMR (as HCl-salt, MeOH-d₄): 2.06-2.18 (m, 1H), 2.22 (s, 3H), 2.26 (s, 3H), 2.56-2.68 (m, 1H), 2.87-3.11 (m, 2H), 4.55 (t, 1H), 6.78 (d, J=7.6 Hz, 1H), 6.99 (d, J=7.6 Hz, 1H), 7.27 (s, 1H), 8.80 (s, 1H)

4-(5,7-Dimethylindan-1-yl)-1H-imidazole

35 ¹H NMR (CDCl₃): 2.07 (s, 3H), 2.07-2.22 (m, 1H), 2.31 (s, 3H), 2.40-2.53 (m, 1H), 2.77-2.87 (m, 1H), 2.94-3.05 (m, 1H), 4.44 (m, 1H), 6.55 (s, 1H), 6.80 (s, 1H), 6.94 (s, 1H), 7.53 (s, 1H)

4-(2,4-Dimethylindan-1-yl)-1H-imidazole

1H NMR (CDCl₃): 1.23 (d, 3H), 2.28 (s, 3H), 2.46-2.55 (m, 2H), 3.05-3.16 (m, 1H), 3.92 (d, 1H), 6.81-6.83 (m, 2H), 6.95-7.09 (m, 2H), 7.56 (s, 1H)

5

4-(5-Methoxyindan-1-yl)-1H-imidazole. M.p. 180-184 °C.

1H NMR (CDCl₃+MeOH-d₄): 2.09-2.19 (m, 1H), 2.48-2.59 (m, 1H), 2.87-2.98 (m, 2H), 3.79 (s, 3H), 4.35 (t, 1H), 6.69-6.73 (m, 2H), 6.82 (d, J=2.0 Hz, 1H), 7.03 (d, J=8.2 Hz, 1H), 7.53 (s, 1H)

10

4-(7-Methoxyindan-1-yl)-1H-imidazole

1H NMR (CDCl₃): 2.20-2.50 (m, 2H), 2.83-2.98 (m, 2H), 3.82 (s, 3H), 4.50-4.54 (m, 1H), 6.66-6.72 (m, 2H), 6.86 (d, J=7.7 Hz, 1H), 7.16 (t, J=7.7 Hz, 1H), 7.43 (s, 1H)

15

4-(5,7-Dimethoxyindan-1-yl)-1H-imidazole

1H NMR (as HCl-salt, MeOH-d₄): 2.09-2.20 (m, 1H), 2.52-2.65 (m, 1H), 2.87-3.11 (m, 2H), 3.69 (s, 1H), 3.78 (s, 1H), 4.49-4.54 (m, 1H), 6.37 (s, 1H), 6.50 (s, 1H), 7.08 (s, 1H), 8.73 (s, 1H)

20

EXAMPLE 2**4-(1-Methylindan-1-yl)-1H-imidazole**

25

a) 2-(3-Benzyl-3H-imidazol-4-yl)-4-phenylbutan-2-ol

1.0 g of magnesium turnings are covered with 5 ml of dry tetrahydrofuran. To the mixture is added 7.8 g of (2-bromoethyl)benzene in 30 ml of dry tetrahydrofuran at such a rate that a smooth reaction is maintained.

30 The mixture is then heated under reflux for one hour. After being cooled to room temperature, 3.0 g of 1-(3-benzyl-3H-imidazol-4-yl)-ethanone in 20 ml of tetrahydrofuran is added dropwise to the Grignard reagent and the reaction mixture is refluxed for one hour. The cooled reaction mixture is poured into a cold dilute hydrochloric acid solution. Work-up of the mixture gives the crude product, which is recrystallized from ethyl acetate. The yield is 3.3 g.

1H NMR (as HCl-salt, MeOH-d₄): 1.67 (s, 3H), 2.01-2.08 (m, 2H), 2.37-2.48 (m, 1H), 2.57-2.71 (m, 1H), 5.75 (dd, 2H), 6.97-7.42 (m, 10H), 7.50 (s, 1H), 8.75 (s, 1H)

b) 2-(1H-Imidazol-4-yl)-4-phenylbutan-2-ol

3.3 g of 2-(3-benzyl-3H-imidazol-4-yl)-4-phenylbutan-2-ol is dissolved in 100 ml of ethanol. The reaction solution is hydrogenated at 50 °C with 10 % palladium on carbon as catalyst for 4.5 hours. Work-up of the reaction mixture gives the crude product, which is recrystallized from ethyl acetate. The yield is 2.0 g.

5 ^1H NMR (MeOH-d₄): 1.56 (s, 3H), 2.01-2.13 (m, 2H), 2.37-2.47 (m, 1H), 2.53-2.64 (m, 1H), 6.96 (s, 1H), 7.07-7.13 (m, 3H), 7.18-7.23 (m, 2H), 7.61 (s, 1H)

10

c) 4-(1-Methylindan-1-yl)-1H-imidazole

A mixture of 2-(1H-imidazol-2-yl)-4-phenylbutan-2-ol (0.5 g) and methanesulfonic acid (12 ml) is heated at 100 °C for 35 minutes. The cooled reaction mixture is poured into water and is made alkaline with sodium hydroxide solution. The product is extracted into ethyl acetate which is washed with water, dried with sodium sulfate and evaporated under reduced pressure. The product is converted to its hydrochloride salt in ethyl acetate using dry hydrochloric acid. The yield is 387 mg, m.p. 164-171 °C.

15 ^1H NMR (as HCl-salt, MeOH-d₄): 1.67 (s, 3H), 2.21-2.30 (m, 1H), 2.40-2.50 (m, 1H), 2.96-3.11 (m, 2H), 7.06-7.33 (m, 5H), 8.84 (s, 1H)

EXAMPLE 3**4-(5-Chloro-1,2,3,4-tetrahydronaphthalen-1-yl)-1H-imidazole**

25

a) 4-(2-Chlorophenyl)-1-(1H-imidazol-4-yl)-butan-1-ol

3.3 g of magnesium turnings are covered with 40 ml of dry tetrahydrofuran. To the mixture is added 32.0 g of 1-(3-bromopropyl)-2-chlorobenzene (prepared according to Baddar, F.G. et al., J. Chem. Soc., 30 1959, 1027) in 100 ml of dry tetrahydrofuran at such a rate that a smooth reaction is maintained. When the magnesium turnings have reacted the solution is cooled to room temperature. 4.3 g of imidazole-4-carbaldehyde in 40 ml of dry tetrahydrofuran is then added dropwise to the Grignard reagent and the reaction mixture is refluxed for one hour. The cooled reaction mixture is poured into a cold dilute hydrochloric acid solution. Tetrahydrofuran is distilled off under reduced pressure and the residue is cooled. The resulting

precipitate is filtered and washed with water. The crude product is recrystallized from ethanol. The yield is 8.0 g. Melting point of the hydrochloride salt is 152-154 °C.

5 ^1H NMR (as HCl-salt, MeOH-d4): 1.65-1.91 (m, 4H), 2.80 (t, 2H), 4.82, (t, 1H),
7.14-7.35 (m, 4H), 7.40 (s, 1H), 8.83 (s, 1H)

b) 4-(5-Chloro-1,2,3,4-tetrahydronaphthalen-1-yl)-1H-imidazole

A mixture of 4-(2-chlorophenyl)-1-(1H-imidazol-4-yl)-butan-1-ol
10 hydrochloride (1.0 g) and methanesulfonic acid (15 ml) is heated at 100 °C for 2 hours. The cooled reaction mixture is poured into water and is made alkaline with sodium hydroxide solution. The product is extracted into ethyl acetate which is washed with water, dried with sodium sulfate and evaporated under reduced pressure. The crude product is recrystallized from ethyl acetate. The
15 yield is 0.4 g, m.p. 165-169 °C.
 ^1H NMR (CDCl₃): 1.74-1.83 (m, 2H), 1.95-2.15 (m, 2H), 2.70-2.91 (m, 2H),
4.19 (t, 1H), 6.49 (s, 1H), 6.96-7.05 (m, 2H), 7.21-7.24 (m, 1H), 7.54 (s, 1H)

EXAMPLE 4

20

4-(1,2,3,4-Tetrahydronaphthalen-1-yl)-1H-imidazole

4-(5-Chloro-1,2,3,4-tetrahydronaphthalen-1-yl)-1H-imidazole (300 mg)
is dissolved in ethanol (15 ml). The reaction solution is hydrogenated at 50 °C
with 10 % palladium on carbon as catalyst for 8 hours. The mixture is filtered to
25 remove the catalyst, and the filtrate is evaporated under reduced pressure.
The residue is dissolved in water and is made alkaline with sodium hydroxide
solution. The product is extracted into methylene chloride which is washed
with water, dried with sodium sulfate and evaporated under reduced pressure.
The crude product is recrystallized from ethyl acetate. The yield is 169 mg.
30 m.p. 105-110 °C.
 ^1H NMR (CDCl₃): 1.70-1.85 (m, 2H), 2.05-2.11 (m, 2H), 2.78-2.86 (m, 2H),
4.21 (t, 1H), 6.59 (s, 1H), 7.04-7.14 (m, 4H), 7.52 (s, 1H)

EXAMPLE 5

3-(1H-Imidazol-4-yl)-5-isobutylindan-1-ol

5

a) 3-(3-Benzyl-3H-imidazol-4-yl)-1-(4-isobutylphenyl)-propen-1-one

A solution of 4-isobutylacetophenone (2.0 g), 3-benzyl-3H-imidazole-4-carbaldehyde (2.1 g) and 48 % sodium hydroxide (0.65 ml) in methanol (20 ml) is heated at 55-60 °C for 6 hours. The reaction mixture is then cooled in an ice bath. The resulting precipitate is filtered, and rinsed with methanol. The yield is 2.5 g.

1 H NMR (CDCl₃): 0.91 (d, 6H), 1.85-1.95 (m, 1H), 2.54 (d, 2H), 5.28 (s, 2H), 7.12-7.14 (m, 2H), 7.23 (d, J=8.2 Hz, 2H), 7.30-7.41 (m, 4H), 7.60-7.68 (m, 3H), 7.80 (d, J=8.2 Hz, 2H)

b) 3-(3-Benzyl-3H-imidazol-4-yl)-5-isobutylindan-1-one

A mixture of 3-(3-benzyl-3H-imidazol-4-yl)-1-(4-isobutylphenyl)-propen-1-one (2.4 g) and methanesulfonic acid (40 ml) is heated at 120°C for 40 minutes. Work-up of the reaction mixture gives the crude product, which is purified by flash chromatography by eluting with methylene chloride-methanol solution. The yield is 0.5 g.

1 H NMR (CDCl₃): 0.89 (d, 6H), 1.81-1.91 (m, 1H), 2.34 (dd, J=18.8 Hz, J=4.0 Hz, 1H), 2.51 (d, 2H), 2.80 (dd, J=18.8 Hz, J=7.9 Hz, 1H), 4.44-4.48 (m, 1H), 5.03-5.16 (m, 2H), 6.64 (s, 1H), 7.05-7.08 (m, 2H), 7.13 (s, 1H), 7.22 (d, J=7.8 Hz, 1H), 7.26-7.39 (m, 3H), 7.57 (s, 1H), 7.68 (d, J=7.8 Hz, 1H)

c) 3-(1H-Imidazol-4-yl)-5-isobutylindan-1-ol

30

3-(3-Benzyl-3H-imidazol-4-yl)-5-isobutylindan-1-one (0.5 g) is dissolved in ethanol (15 ml). The reaction solution is hydrogenated at 50 °C with 10 % palladium on carbon as catalyst until no more hydrogen is consumed. The mixture is filtered to remove the catalyst, and the filtrate is evaporated under reduced pressure. The crude product contains cis- and trans-isomers. The isomers are purified by flash chromatography.

1 H NMR (cis-isomer, CDCl₃): 0.85 (d, 6H), 1.74-1.84 (m, 1H), 2.15-2.20 (m, 1H), 2.40 (d, 2H), 2.69-2.79 (m, 1H), 4.33 (d, 1H), 5.16 (d, 1H), 6.91 (s, 1H), 6.93 (s, 1H), 7.02 (d, J=7.7 Hz, 1H), 7.39 (d, J=7.7 Hz, 1H), 7.42 (s, 1H)

¹H NMR (trans-isomer, CDCl₃): 0.85 (d, 6H), 1.74-1.84 (m, 1H), 2.35-2.46 (m, 4H), 4.60 (t, 1H), 5.26 (t, 1H), 6.65 (s, 1H), 6.95 (s, 1H), 7.04 (d, J=7.7 Hz, 1H), 7.33 (d, J=7.7 Hz, 1H), 7.46 (s, 1H)

5 EXAMPLE 6

3-(1H-Imidazol-4-yl)-5-methoxy-6,7-dimethylindan-1-one

a) 3-(3-Benzyl-3H-imidazol-4-yl)-5-methoxy-6,7-dimethylindan-1-one

10 A mixture of 2,3-dimethylanisole (2.0 g), 3-(3-benzyl-3H-imidazol-4-yl)-acrylic acid (3.4 g) and methanesulfonic acid (60 ml) is heated at 90-95 °C for 45 minutes. The cooled reaction mixture is poured into water and is made alkaline with sodium hydroxide solution. The product is extracted into ethyl acetate which is washed with water, dried with sodium sulfate and evaporated in reduced pressure. The crude product is purified by flash chromatography by eluting with methylene chloride-methanol solution. The yield is 1.1 g.

15 1H NMR (CDCl₃): 2.13 (s, 3H), 2.35 (dd, J=18.5 Hz, J=4.1 Hz, 1H), 2.61 (s, 3H), 2.81 (dd, J=18.5 Hz, J=8.2 Hz, 1H), 3.76 (s, 3H), 4.34-4.38 (m, 1H), 5.05 (s, 2H), 6.52 (s, 1H), 6.72 (s, 1H), 7.00-7.05 (m, 2H), 7.29-7.36 (m, 3H), 7.56 (s, 1H)

b) 3-(1H-Imidazol-4-yl)-5-methoxy-6,7-dimethylindan-1-one

25 3-(3-Benzyl-3H-imidazol-4-yl)-5-methoxy-6,7-dimethylindan-1-one (1.1 g) is dissolved in ethanol (90 ml). The reaction solution is hydrogenated at 50-55 °C with 10 % palladium on carbon as catalyst for 7 hours. The mixture is filtered to remove the catalyst, and the filtrate is evaporated under reduced pressure. The product is converted to its hydrochloride salt in ethyl acetate using dry hydrochloric acid. The yield is 0.6 g, m.p. 258-261 °C.

30 1H NMR (as HCl-salt, MeOH-d₄): 2.16 (s, 3H), 2.62 (s, 3H), 2.68 (dd, J=18.7 Hz, J=4.0 Hz, 1H), 3.18 (dd, J=18.7 Hz, J=8.3 Hz, 1H), 3.87 (s, 3H), 4.77-4.81 (m, 1H), 6.81 (s, 1H), 7.43 (s, 1H), 8.85 (s, 1H)

35 Using the same method the following compound was prepared:

3-(1H-Imidazol-4-yl)-5-methoxy-4,7-dimethylindan-1-one

¹H NMR (CDCl₃): 1.96 (s, 3H), 2.64 (dd, J=18.6 Hz, J=2.1 Hz, 1H), 2.65 (s,

- 5 3H), 3.13 (dd, J=18.6 Hz, J=8.4 Hz, 1H), 3.90 (s, 3H), 4.57-4.61 (m, 1H), 6.47 (s, 1H), 6.68 (s, 1H), 7.50 (s, 1H)

EXAMPLE 7**10 3-(1H-Imidazol-4-yl)-5-methoxy-6,7-dimethylindan-1-ol**

3-(1H-Imidazol-4-yl)-5-methoxy-6,7-dimethylindan-1-one (0.53 g) is dissolved in ethanol (30 ml) and 0.3 g of sodium borohydride is added. The mixture is stirred at 35-40 °C for 7 hours. About 20 ml of ethanol is then distilled off and 15 30 ml of water is added. The solution is extracted with ethyl acetate. The combined ethyl acetate extracts are washed with water, dried with sodium sulfate, and evaporated under reduced pressure. The product is the mixture of cis- and trans-isomers (about 85:15). Crystallization of the product from ethyl acetate gives a cis-isomer, m.p. 184-189 °C.

- 20 ¹H NMR (cis-isomer, CDCl₃): 2.09-2.14 (m, 1H), 2.11 (s, 3H), 2.38 (s, 3H), 2.69-2.77 (m, 1H), 3.73 (s, 3H), 4.31 (d, 1H), 5.26 (d, 1H), 6.48 (s, 1H), 6.90 (s, 1H), 7.43 (s, 1H)

EXAMPLE 8

25

4-(6-Methoxy-4,5-dimethylindan-1-yl)-1H-imidazole

- 30 3-(1H-Imidazol-4-yl)-5-methoxy-6,7-dimethylindan-1-one (0.29 g) is dissolved in the mixture of ethanol (30 ml) and concentrated hydrochloric acid (0.2 ml). The solution is hydrogenated at 50-55 °C with 10 % palladium on carbon as catalyst until no more hydrogen is consumed. The mixture is filtered and the filtrate is evaporated to dryness. The residue is crystallized from the mixture of ethyl acetate and ethanol. M.p. of the hydrochloride salt is 174-177 °C.

35 ¹H NMR (as HCl-salt, MeOH-d₄): 2.05-2.17 (m, 1H), 2.11 (s, 3H), 2.21 (s, 3H), 2.54-2.66 (m, 1H), 2.82-3.05 (m, 2H), 3.71 (s, 3H), 4.55 (t, 1H), 6.50 (s, 1H), 7.27 (s, 1H), 8.79 (s, 1H)

Using the same method the following compound was prepared:

4-(6-Isobutylindan-1-yl)-1H-imidazole

¹H NMR (as HCl-salt, MeOH-d₄): 0.86 (d, 6H), 1.73-1.83 (m, 1H), 2.11-2.18 (m, 1H), 2.42 (d, 2H), 2.58-2.65 (m, 1H), 2.97-3.31 (m, 2H), 4.56 (t, 1H), 6.85 (s, 1H), 7.04 (d, J=7.6 Hz, 1H), 7.22 (d, J=7.6 Hz, 1H), 7.30 (s, 1H), 8.83 (s, 1H)

5

EXAMPLE 9**3-(1H-Imidazol-4-yl)-6,7-dimethylindan-5-ol**

10 A stirred mixture of 4-(6-methoxy-4,5-dimethylindan-1-yl)-1H-imidazole hydrochloride (0.29 g) and hydrobromic acid (15 ml) is heated under reflux for 40 minutes. The cooled reaction mixture is poured into water and is made basic with ammonium hydroxide solution. The product is extracted into ethyl acetate which is washed with water, dried with sodium sulfate and evaporated to dryness. The crude product is purified by flash chromatography and crystallized from ethyl acetate. M.p. 198-202 °C.

15 ¹H NMR (CDCl₃+MeOH-d₄): 2.02-2.13 (m, 1H), 2.13 (s, 3H), 2.18 (s, 3H), 2.43-2.54 (m, 1H), 2.71-2.82 (m, 1H), 2.86-2.96 (m, 1H), 4.33 (t, 1H), 6.49 (s, 1H), 6.75 (s, 1H), 7.50 (s, 1H)

20

Using the same method the following compound was prepared:

5-Hydroxy-3-(1H-imidazol-4-yl)-6,7-dimethylindan-1-one

1H NMR (MeOH-d₄): 2.12 (s, 3H), 2.58 (s, 3H), 2.67 (dd, J=18.4 Hz, J=4.1 Hz, 1H), 3.02 (dd, J=18.4 Hz, J=8.0 Hz, 1H), 4.43-4.47 (m, 1H), 6.59 (s, 1H), 6.90 (s, 1H), 7.62 (s, 1H)

1-(1H-Imidazol-4-yl)-indan-5-ol. M.p. 210-220 °C.

1H NMR(MeOH-d₄): 2.04-2.17 (m, 1H), 2.41-2.52 (m, 1H), 2.77-2.97 (m, 2H),

30 4.27 (t, 1H), 6.55 (dd, J=8.1 Hz, J=2.3 Hz, 1H), 6.67 (d, J=2.3 Hz, 1H), 6.70 (s, 1H), 6.84 (d, J=8.1 Hz, 1H), 7.57 (s, 1H)

3-(1H-Imidazol-4-yl)-indan-4-ol. M.p. 142-145 °C.

1H NMR (CDCl₃+MeOH-d₄): 2.13-2.26 (m, 1H), 2.49-2.60 (m, 1H), 2.89-3.08

35 (m, 2H), 4.54 (t, 1H), 6.71-6.76 (m, 3H), 7.06 (t, J=7.6 Hz, 1H), 7.55 (s, 1H)

3-(1H-Imidazol-4-yl)-indan-4,6-diol

- 5 ^1H NMR (MeOH-d₄): 2.10-2.21 (m, 1H), 2.39-2.51 (m, 1H), 2.71-2.95 (m, 2H),
4.34-4.39 (m, 1H), 6.10 (d, J=1.9 Hz, 1H), 6.20 (d, J=1.9 Hz, 1H), 6.64 (s, 1H),
7.59 (s, 1H)

EXAMPLE 10**10 4-(3-Ethoxy-6-methoxy-4,5-dimethylindan-1-yl)-1H-imidazole (cis-isomer)**

3-(1H-Imidazol-4-yl)-5-methoxy-6,7-dimethylindan-1-ol (cis-isomer, 0.1 g) is dissolved in the mixture of ethanol (20 ml) and concentrated hydrochloric acid (2 ml). The solution is stirred at 25 °C for one hour. Work-up of the reaction

15 mixture gives the crude product, which is purified by flash chromatography using methylene chloride-methanol as eluent.

1H NMR (CDCl₃): 1.31 (t, J=7.0 Hz, 3H), 2.12 (s, 3H), 2.20-2.25 (m, 1H), 2.32 (s, 3H), 2.51-2.60 (m, 1H), 3.72 (q, J=7.0 Hz, 2H), 3.73 (s, 3H), 4.40 (d, 1H), 4.96 (d, 1H), 6.52 (s, 1H), 6.93 (s, 1H), 7.41 (s, 1H)

20

EXAMPLE 11**4-(Indan-1-yl)-1H-imidazole****25 a) 4-(3H-Inden-1-yl)-1H-imidazole**

To a stirred solution of 1-(N,N-dimethylsulfamoyl)-1H-imidazole (1.9 g, prepared according to Chadwick, D.J. and Ngochindo, R.I., J. Chem. Soc., Perkin Trans. I 1984, 481) in dry tetrahydrofuran (90 ml) at -70 °C under nitrogen, is added dropwise 2.5 M butyllithium in hexane (5.1 ml). After 30 minutes tert-butyldimethylsilyl chloride (2.0 g) in dry tetrahydrofuran (5 ml) is added and the mixture is allowed to warm to 25 °C. After 1.5 hours the mixture is again cooled to -70 °C and treated with 2.5 M butyllithium in hexane (5.3 ml). After 30 minutes, 1-indanone (2.1 g) in dry tetrahydrofuran (5 ml) is added 30 and the mixture is allowed to warm to room temperature. The reaction mixture is then quenched with saturated Na₂CO₃ solution (2 ml), and the solvent is removed under reduced pressure. The residue is dissolved in methylene chloride and washed with water, dried with sodium sulfate and evaporated to dryness under reduced pressure. The bis-protected intermediate is refluxed

with 2 N hydrochloric acid (200 ml) for 2 hours. The cooled solution is made basic by ammonium hydroxide solution, and extracted with methylene chloride. The organic layer is washed with water, dried with sodium sulfate and the solvent removed under reduced pressure. The crude product is

5 purified by flash chromatography using methylene chloride-methanol as eluent. The product is converted to the hydrochloride salt in ethyl acetate-ethanol solution, m.p. 232-240 °C.

¹H NMR (as HCl-salt, MeOH-d₄): 3.66 (d, 2H), 7.07 (t, 1H), 7.31-7.43 (m, 2H), 7.59 (d, 1H), 7.68 (d, 1H), 8.03 (s, 1H), 9.06 (s, 1H)

10

b) 4-(Indan-1-yl)-1H-imidazole

4-(3H-Inden-1-yl)-1H-imidazole hydrochloride (80 mg) is dissolved in ethanol (6 ml). The reaction solution is hydrogenated at 40-50 °C with 10 % palladium on carbon as catalyst until no more hydrogen is consumed. Work-up of the reaction mixture gives the crude product which is purified by flash chromatography using methylene chloride-methanol as eluent.

¹H NMR (CDCl₃): 2.08-2.19 (m, 1H), 2.41-2.51 (m, 1H), 2.80-2.95 (m, 2H), 4.37 (t, 1H), 6.65 (s, 1H), 7.07-7.21 (m, 4H), 7.25 (s, 1H)

20

Using the same method the following compound was prepared:

4-(6-Methoxyindan-1-yl)-1H-imidazole

¹H NMR (as HCl-salt, MeOH-d₄): 2.08-2.20 (m, 1H), 2.56-2.67 (m, 1H), 2.80-2.97 (m, 2H), 3.72 (s, 3H), 4.53 (t, 1H), 6.71 (d, J=1.9 Hz, 1H), 6.75 (dd, J=8.3 Hz, J=1.9 Hz, 1H), 6.92 (s, 1H), 7.15 (d, J=8.3 Hz, 1H), 8.82 (s, 1H)

EXAMPLE 12

30 4-(Indan-1-ylmethyl)-1H-imidazole

Titanium tetrachloride (17.2 g) is added dropwise to a stirred suspension of zinc powder (11.9 g) in tetrahydrofuran (100 ml) with ice cooling under a nitrogen atmosphere. The mixture is heated at reflux for one hour. After being 35 cooled to room temperature, 1-indanone (2.0 g) and 3-benzyl-3H-imidazole-4-carbaldehyde (4.2 g) in tetrahydrofuran (30 ml) are added into the mixture.

The mixture is refluxed with stirring for 3 hours. The cooled reaction mixture is made alkaline with dilute sodium hydroxide solution. The slurry is filtered, and the filtrate is evaporated to dryness under reduced pressure. The residue,

which contains the crude intermediate 1-benzyl-5-(indan-1-ylidenemethyl)-1H-imidazole is purified by flash chromatography.

The purified intermediate (0.8 g) is dissolved in the mixture of ethanol (30 ml),
5 water (2 ml) and concentrated hydrochloric acid (0.5 ml). The reaction mixture
is hydrogenated at 50-60 °C with 10 % palladium on carbon as catalyst until
no more hydrogen is consumed. The mixture is filtered, and the filtrate is
evaporated to dryness. The residue is dissolved in water and is made alkaline
with sodium hydroxide. The product is then extracted into methylene chloride
10 which is washed with water, dried with sodium sulfate and evaporated to
dryness. The product is converted to its hydrochloride salt in ethyl acetate
using dry hydrochloric acid. The yield is 0.5 g, m.p. 182-183 °C.
15 ^1H NMR (as HCl-salt, MeOH-d₄): 1.74-1.81 (m, 1H), 2.22-2.29 (m, 1H), 2.80-
2.95 (m, 3H), 3.17 (dd, J=15.1 Hz, J=5.7 Hz, 1H), 3.48-3.53 (m, 1H), 7.12-7.23
(m, 4H), 7.26 (s, 1H), 8.79 (s, 1H).

Using the same method the following compounds were prepared:

4-(6-Methoxyindan-1-ylmethyl)-1H-imidazole. M.p. of hydrochloride 197-200
20 °C.
 ^1H NMR (as HCl-salt, MeOH-d₄): 1.72-1.84 (m, 1H), 2.19-2.31 (m, 1H), 2.70-
2.89 (m, 3H), 3.16 (dd, J=14.9 Hz, J=5.5 Hz, 1H), 3.42-3.51 (m, 1H), 3.74 (s,
3H), 6.68 (d, J=2.2 Hz, 1H), 6.74 (dd, J=8.2 Hz, J=2.2 Hz, 1H), 7.10 (d, J=8.2
Hz, 1H), 7.27 (s, 1H), 8.82 (s, 1H)

25 4-(5-Methoxyindan-1-ylmethyl)-1H-imidazole. M.p. of hydrochloride 204-206
°C.
 ^1H NMR (as HCl-salt, MeOH-d₄): 1.71-1.83 (m, 1H), 2.19-2.31 (m, 1H), 2.75-
2.94 (m, 3H), 3.13 (dd, J=15.0 Hz, J=5.5 Hz, 1H), 3.40-3.49 (m, 1H), 3.75 (s,
3H), 6.70 (dd, J=8.3 Hz, J=2.2 Hz, 1H), 6.78 (d, J=2.2 Hz, 1H), 7.00 (d, J=8.3
Hz, 1H), 7.26 (s, 1H), 8.82 (s, 1H)

30 4-(5,6-Dimethoxyindan-1-ylmethyl)-1H-imidazole. M.p. of hydrochloride 193-
197 °C.
35 ^1H NMR (as HCl-salt, MeOH-d₄): 1.72-1.84 (m, 1H), 2.20-2.32 (m, 1H), 2.75-
2.88 (m, 3H), 3.15 (dd, J=15.1 Hz, J=5.2 Hz, 1H), 3.41-3.50 (m, 1H), 3.77 (s,
3H), 3.79 (s, 3H), 6.73 (s, 1H), 6.84 (s, 1H), 7.26 (s, 1H), 8.82 (s, 1H)

4-(6-Methoxy-4,5-dimethylindan-1-ylmethyl)-1H-imidazole. M.p. of hydrochloride 194-197 °C.

¹H NMR (as HCl-salt, MeOH-d₄): 1.70-1.81 (m, 1H), 2.09 (s, 3H), 2.15 (s, 3H), 2.17-2.29 (m, 1H), 2.69-2.89 (m, 3H), 3.14 (dd, J=15.1 Hz, J=5.7 Hz, 1H), 3.42-

5 3.50 (m, 1H), 3.74 (s, 3H), 6.54 (s, 1H), 7.24 (s, 1H), 8.81 (s, 1H)

4-(6-Methoxy-4,7-dimethylindan-1-ylmethyl)-1H-imidazole. M.p. of hydrochloride 168-175 °C.

¹H NMR (as HCl-salt, MeOH-d₄): 1.88-1.94 (m, 1H), 2.07 (s, 3H), 2.09-2.18 (m,

10 1H), 2.19 (s, 3H), 2.69-2.77 (m, 3H), 2.90 (dd, J=15.2 Hz, J=4.7 Hz, 1H), 3.51-3.57 (m, 1H), 3.77 (s, 3H), 6.60 (s, 1H), 7.21 (s, 1H), 8.80 (s, 1H)

4-(6-Methoxy-5-methylindan-1-ylmethyl)-1H-imidazole. M.p. of hydrochloride 183-186 °C.

¹H NMR (as HCl-salt, MeOH-d₄): 1.71-1.82 (m, 1H), 2.13 (s, 3H), 2.18-2.29 (m, 1H), 2.70-2.89 (m, 3H), 3.16 (dd, J=15.0 Hz, J=5.4 Hz, 1H), 3.42-3.50 (m, 1H), 3.76 (s, 3H), 6.65 (s, 1H), 6.95 (s, 1H), 7.26 (s, 1H), 8.82 (s, 1H)

4-(6-Fluoroindan-1-ylmethyl)-1H-imidazole. M.p. of hydrochloride 215-222 °C.

¹H NMR (as HCl-salt, MeOH-d₄): 1.76-1.88 (m, 1H), 2.23-2.35 (m, 1H), 2.76-

20 2.92 (m, 3H), 3.18 (dd, J=15.3 Hz, J=5.3 Hz, 1H), 3.46-3.56 (m, 1H), 6.86-6.92 (m, 2H), 7.17-7.20 (m, 1H), 7.31 (s, 1H), 8.83 (s, 1H)

4-(5-Fluoroindan-1-ylmethyl)-1H-imidazole. M.p. of hydrochloride 185-189 °C.

¹H NMR (as HCl-salt, MeOH-d₄): 1.76-1.88 (m, 1H), 2.23-2.35 (m, 1H), 2.79-

25 2.98 (m, 3H), 3.16 (dd, J=15.3 Hz, J=5.3 Hz, 1H), 3.43-3.53 (m, 1H), 6.83-6.96 (m, 2H), 7.08-7.13 (m, 1H), 7.29 (s, 1H), 8.82 (s, 1H)

4-(4-Methoxyindan-1-ylmethyl)-1H-imidazole. M.p. of hydrochloride 202-210 °C.

30 ¹H-NMR (as HCl-salt, MeOH-d₄): 1.73-1.82 (m, 1H), 2.18-2.30 (m, 1H), 2.72-2.89 (m, 3H), 3.14 (dd, J=15.0 Hz, J=5.5 Hz, 1H), 3.48-3.56 (m, 1H), 3.80 (s, 3H), 6.72-6.78 (m, 2H), 7.14 (t, 1H), 7.24 (s, 1H), 8.79 (s, 1H)

4-(6-Methoxy-7-methylindan-1-ylmethyl)-1H-imidazole. M.p. of hydrochloride

35 152-158 °C.

¹H NMR (as HCl-salt, MeOH-d₄): 1.86-1.93 (m, 1H), 2.11 (s, 3H), 2.12-2.20 (m, 1H), 2.68-2.96 (m, 4H), 3.52-3.59 (m, 1H), 3.79 (s, 3H), 6.75 (d, J=8.2 Hz, 1H), 6.99 (d, J=8.2 Hz, 1H), 7.22 (s, 1H), 8.79 (s, 1H)

4-(7-Methoxyindan-1-ylmethyl)-1H-imidazole

¹H NMR (as HCl-salt, MeOH-d₄): 1.82-1.90 (m, 1H), 2.09-2.19 (m, 1H), 2.72-2.91 (m, 3H), 3.14 (dd, J=14.9 Hz, J=4.8 Hz, 1H), 3.59-3.74 (m, 1H), 3.76 (s, 3H), 6.72-6.80 (m, 2H), 6.96 (s, 1H), 7.13 (t, 1H), 8.38 (s, 1H)

4-(5,6-Dimethoxy-3,3-dimethylindan-1-ylmethyl)-1H-imidazole

¹H NMR (CDCl₃): 1.12 (s, 3H), 1.28 (s, 3H), 1.63 (dd, J=12.5 Hz, J=8.3 Hz, 1H), 2.09 (dd, J=12.5 Hz, J=7.5 Hz, 1H), 2.72 (dd, J=14.6 Hz, J=9.0 Hz, 1H), 3.16 (dd, J=14.6 Hz, J=5.5 Hz, 1H), 3.47-3.52 (m, 1H), 3.78 (s, 3H), 3.86 (s, 3H), 6.61 (s, 1H), 6.66 (s, 1H), 6.82 (s, 1H), 7.58 (s, 1H)

4-(5-tert-Butylindan-1-ylmethyl)-1H-imidazole

¹H NMR (CDCl₃): 1.32 (s, 9H), 1.71-1.83 (m, 1H), 2.19-2.30 (m, 1H), 2.73-2.87 (m, 3H), 3.08 (dd, J=14.7 Hz, J=5.6 Hz, 1H), 3.44-3.53 (m, 1H), 6.81 (s, 1H), 7.09 (d, J=7.8 Hz, 1H), 7.20 (dd, J=7.8 Hz, J=1.5 Hz, 1H), 7.26 (d, J=1.5 Hz, 1H), 7.55 (s, 1H)

4-(6-Methoxy-3,3-dimethylindan-1-ylmethyl)-1H-imidazole

¹H NMR (CDCl₃): 1.11 (s, 3H), 1.27 (s, 3H), 1.63 (dd, J=12.5 Hz, J=8.9 Hz, 1H), 2.06 (dd, J=12.5 Hz, J=7.5 Hz, 1H), 2.72 (dd, J=14.7 Hz, J=9.0 Hz, 1H), 3.19 (dd, J=14.7 Hz, J=5.4 Hz, 1H), 3.47-3.55 (m, 1H), 3.74 (s, 3H), 6.67 (d, J=2.2 Hz, 1H), 6.74 (dd, J=8.2 Hz, J=2.2 Hz, 1H), 6.83 (s, 1H), 7.03 (d, J=8.2 Hz, 1H), 7.58 (s, 1H)

25

EXAMPLE 13**4-[1-(Indan-1-yl)-ethyl]-1H-imidazole**

30 The procedure of Example 12 is repeated except that 1-(3-benzyl-3H-imidazol-4-yl)-ethanone is used in place of 3-benzyl-3H-imidazole-4-carbaldehyde. The product contains two diastereomers ad and bc (78 % of ad and 22 % of bc).

¹H NMR (as HCl-salt, MeOH-d₄): 1.23 (d, J=7.1 Hz, -CH₃, bc diastereomer),

35 1.38 (d, J=7.1 Hz, -CH₃, ad diastereomer), 1.81-2.32 (m, 2H), 2.70-2.87 (m, 2H), 3.29-3.39 (m, 1H), 3.47-3.57 (m, 1H), 6.98-7.30 (m, 5H), 8.77 (s, 1H, ad diastereomer), 8.84 (s, 1H, bc diastereomer)

Using the same method the following substituted derivative was prepared:

4-[1-(6-Methoxyindan-1-yl)-ethyl]-1H-imidazole

- The reaction mixture contains two diastereomers ad and bc, which are
5 separated by flash chromatography eluting with methylene chloride -
methanol solution.
- 1H NMR (ad diastereomer as HCl-salt, MeOH-d4): 1.37 (d, J=7.1 Hz, 3H),
1.83-1.94 (m, 1H), 2.20-2.33 (m, 1H), 2.58-2.77 (m, 2H), 3.30-3.39 (m, 1H),
3.43-3.49 (m, 1H), 3.74 (s, 3H), 6.63 (d, J=2.4 Hz, 1H), 6.73 (dd, J=8.2 Hz,
10 J=2.4 Hz, 1H), 7.05 (d, J=8.2 Hz, 1H), 7.13 (s, 1H), 8.74 (s, 1H)
- 1H NMR (bc diastereomer as HCl-salt, MeOH-d4): 1.23 (d, J=7.1 Hz, 3H),
1.90-2.01 (m, 1H), 2.05-2.16 (m, 1H), 2.70-81 (m, 2H), 3.29-3.39 (m, 1H), 3.43-
3.54 (m, 1H), 3.72 (s, 3H), 6.54 (d, J=2.4 Hz, 1H), 6.73 (dd, J=8.2 Hz, J=2.4 Hz,
1H), 7.11 (d, J=8.2 Hz, 1H), 7.32 (s, 1H), 8.84 (s, 1H)

15

EXAMPLE 14**4-(5-tert-Butyl-6-methoxyindan-1-ylmethyl)-1H-imidazole**

- 20 Sulfuric acid (0.5 ml) is added into the mixture of 4-(6-methoxyindan-1-ylmethyl)-1H-imidazole hydrochloride (50 mg) and tert-butanol (2 ml). The mixture is stirred at 35-40 °C for 10 hours. The reaction mixture is then poured into water and is made alkaline with sodium hydroxide. The product is extracted into methylene chloride which is washed with water, dried with
25 sodium sulfate and evaporated to dryness. The residue consisting of crude product is converted to its hydrochloride salt in ethyl acetate. The yield is 23 mg, m.p. 174-184 °C.
- 1H NMR (as HCl-salt, MeOH-d4): 1.33 (s, 9H), 1.71-1.83 (m, 1H), 2.19-2.31 (m, 1H), 2.73-2.89 (m, 3H), 3.15 (dd, J=15.0 Hz, J=5.1 Hz, 1H), 3.40-3.50 (m, 1H),
30 3.77 (s, 3H), 6.69 (s, 1H), 7.11 (s, 1H), 7.27 (s, 1H), 8.81 (s, 1H)

Using the same method the following compound was prepared:

4-(6-tert-Butyl-5-methoxyindan-1-ylmethyl)-1H-imidazole

- 35 1H NMR (as HCl-salt, MeOH-d4): 1.30 (s, 9H), 1.73-1.84 (m, 1H), 2.21-2.33 (m, 1H), 2.75-2.94 (m, 3H), 3.05 (dd, J=14.9 Hz, J=6.3 Hz, 1H), 3.35-3.45 (m, 1H),
3.80 (s, 3H), 6.83 (s, 1H), 6.86 (s, 1H), 7.23 (s, 1H), 8.81 (s, 1H)

5,7-Di-tert-butyl-1-(1H-imidazol-4-ylmethyl)-indan-4-ol

¹H NMR (as HCl-salt, MeOH-d₄): 1.39 (s, 9H), 1.41 (s, 9H), 1.87-1.93 (m, 1H), 2.01-2.06 (m, 1H), 2.66-2.75 (m, 3H), 2.89-2.95 (m, 1H), 3.82-3.89 (m, 1H),

5 7.15 (s, 1H), 7.33 (s, 1H), 8.77 (s, 1H)

6-tert-Butyl-1-(1H-imidazol-4-yl)-indan-5-ol

¹H NMR (as HCl-salt, MeOH-d₄): 1.32 (s, 9H), 2.06-2.15 (m, 1H), 2.52-2.63 (m, 1H), 2.82-3.02 (m, 2H), 4.46 (t, 1H), 6.69 (s, 1H), 6.88 (s, 1H), 7.25 (s, 1H), 8.79

10 (s, 1H)

4-(6-tert-Butyl-4-methylindan-1-yl)-1H-imidazole. M.p. of hydrochloride 235-242°C.

¹H NMR (as HCl-salt, MeOH-d₄): 1.25 (s, 9H), 2.09-2.19 (m, 1H), 2.57-2.67

15 (m, 1H), 2.84-3.07 (m, 2H), 4.55 (t, 1H), 6.91 (s, 1H), 7.12 (s, 1H), 7.25 (s, 1H), 8.74 (s, 1H)

5,7-Di-tert-Butyl-3-(1H-imidazol-4-yl)-indan-4-ol. M.p. of hydrochloride 216-222°C.

20 ¹H NMR (as HCl-salt, MeOH-d₄): 1.35 (s, 9H), 1.39 (s, 9H), 2.11-2.18 (m, 1H), 2.44-2.52 (m, 1H), 3.06-3.16 (m, 2H), 4.59-4.63 (m, 1H), 6.78 (s, 1H), 7.23 (s, 1H), 8.75 (s, 1H)

EXAMPLE 15

25

3-(1H-Imidazol-4-ylmethyl)-indan-5-ol

A stirred mixture of 4-(6-methoxyindan-1-ylmethyl)-1H-imidazole

hydrochloride (140 mg) and 48 % hydrobromic acid (7 ml) is heated under

30 reflux for 45 minutes. The cooled reaction mixture is poured into water and is made basic with ammonium hydroxide solution. The product is extracted into ethyl acetate which is washed with water, dried with sodium sulfate and evaporated to dryness. The crude product is converted to its hydrochloride salt in ethyl acetate. M.p. 206-208 °C.

35 ¹H NMR (as HCl-salt, MeOH-d₄): 1.70-1.81 (m, 1H), 2.18-2.29 (m, 1H), 2.70-2.88 (m, 3H), 3.12 (dd, J=15.3 Hz, J=5.8 Hz, 1H), 3.38-3.46 (m, 1H), 6.53 (d, J =2.2 Hz, 1H), 6.60 (dd, J=8.1 Hz, J=2.2 Hz, 1H), 7.01 (d, J=8.1 Hz, 1H), 7.27 (s, 1H), 8.81 (s, 1H)

Using the same method the following compounds were prepared:

1-(1H-Imidazol-4-ylmethyl)-indan-5-ol. M.p. of hydrochloride 159-161 °C.

¹H NMR (as HCl-salt, MeOH-d₄): 1.69-1.80 (m, 1H), 2.17-2.29 (m, 1H), 2.71-

5 2.89 (m, 3H), 3.11 (dd, J=14.8 Hz, J=5.7 Hz, 1H), 3.35-3.45 (m, 1H), 6.57 (dd, J=8.1 Hz, J=2.2 Hz, 1H), 6.64 (d, J=2.2 Hz, 1H), 6.89 (d, J=8.1 Hz, 1H), 7.24 (s, 1H), 8.79 (s, 1H)

1-(1H-Imidazol-4-ylmethyl)-indan-5,6-diol

10 ¹H NMR (as HCl-salt, MeOH-d₄): 1.67-1.78 (m, 1H), 2.15-2.27 (m, 1H), 2.65-2.85 (m, 3H), 3.05 (dd, J=15.1 Hz, J=5.8 Hz, 1H), 3.30-3.40 (m, 1H), 6.51 (s, 1H), 6.63 (s, 1H), 7.24 (s, 1H), 8.80 (s, 1H)

6-tert-Butyl-3-(1H-imidazol-4-ylmethyl)-indan-5-ol

15 ¹H NMR (as HCl-salt, MeOH-d₄): 1.35 (s, 9H), 1.69-1.79 (m, 1H), 2.18-2.28 (m, 1H), 2.69-2.86 (m, 3H), 3.08 (dd, J=15.0 Hz, J=6.0 Hz, 1H), 3.35-3.43 (m, 1H), 6.46 (s, 1H), 7.04 (s, 1H), 7.26 (s, 1H), 8.81 (s, 1H)

6-tert-Butyl-1-(1H-imidazol-4-ylmethyl)-indan-5-ol. M.p. of hydrochloride 229-

20 230 °C.

¹H NMR (as HCl-salt, MeOH-d₄): 1.32 (s, 9H), 1.72-1.81 (m, 1H), 2.18-2.29 (m, 1H), 2.72-2.87 (m, 3H), 3.03 (dd, J=15.1 Hz, J=6.5 Hz, 1H), 3.32-3.40 (m, 1H), 6.59 (s, 1H), 6.79 (s, 1H), 7.23 (s, 1H), 8.81 (s, 1H)

25 3-(1H-Imidazol-4-ylmethyl)-6,7-dimethylindan-5-ol. M.p. of hydrochloride 229-238 °C.

¹H NMR (as HCl-salt, MeOH-d₄): 1.66-1.78 (m, 1H), 2.08 (s, 3H), 2.13 (s, 3H), 2.14-2.26 (m, 1H), 2.66-2.85 (m, 3H), 3.06 (dd, J=15.1 Hz, J=5.8 Hz, 1H), 3.35-3.43 (m, 1H), 6.39 (s, 1H), 7.22 (s, 1H), 8.79 (s, 1H)

30

3-(1H-Imidazol-4-ylmethyl)-4,7-dimethylindan-5-ol

¹H NMR (as HCl-salt, MeOH-d₄): 1.85-1.93 (m, 1H), 2.07 (s, 3H), 2.11 (s, 3H), 2.11-2.20 (m, 1H), 2.65-2.77 (m, 3H), 2.90 (dd, J=15.1 Hz, J=4.6 Hz, 1H), 3.49-3.57 (m, 1H), 6.47 (s, 1H), 7.19 (s, 1H), 8.79 (s, 1H)

35

3-[1-(1H-Imidazol-4-yl)-ethyl]-indan-5-ol (mixture of two diastereomers ad and bc)

¹H NMR (base, CDCl₃+MeOH-d₄): 1.12 (d, J=7.0 Hz, -CH₃, ad diastereomer), 1.22 (d, J=7.1 Hz, -CH₃, bc diastereomer)

3-(1H-Imidazol-4-ylmethyl)-6-methylindan-5-ol

¹H NMR (as HCl-salt, MeOH-d₄): 1.68-1.79 (m, 1H), 2.13 (s, 3H), 2.15-2.27 (m, 1H), 2.68-2.86 (m, 3H), 3.08 (dd, J=15.3 Hz, J=5.8 Hz, 1H), 3.36-3.43 (m, 1H),

5 6.49 (s, 1H), 6.90 (s, 1H), 7.25 (s, 1H), 8.81 (s, 1H)

1-(1H-Imidazol-4-ylmethyl)-indan-4-ol. M.p. 199-205 °C.

¹H NMR (MeOH-d₄): 1.68-1.80 (m, 1H), 2.10-2.22 (m, 1H), 2.60-2.86 (m, 3H), 3.00 (dd, J=14.6 Hz, J=5.3 Hz, 1H), 3.38-3.48 (m, 1H), 6.56 (d, J=7.8 Hz, 1H), 6.62 (d, J=7.8 Hz, 1H), 6.71 (s, 1H), 6.94 (t, J=7.8 Hz, 1H), 7.56 (s, 1H)

10

3-(1H-Imidazol-4-ylmethyl)indan-4-ol

¹H NMR (as HCl-salt, MeOH-d₄): 1.78-1.87 (m, 1H), 2.12-2.22 (m, 1H), 2.78-2.92 (m, 3H), 3.24 (dd, J=15.3 Hz, J=5.3 Hz, 1H), 3.59-3.65 (m, 1H), 6.56 (d, J=7.7 Hz, 1H), 6.68 (d, J=7.7 Hz, 1H), 6.99 (t, J=7.7 Hz, 1H), 7.15 (s, 1H), 8.75 (s, 1H)

15

3-(1H-Imidazol-4-ylmethyl)-1,1-dimethylindan-5,6-diol

¹H NMR (MeOH-d₄): 1.09 (s, 3H), 1.24 (s, 3H), 1.54 (dd, J=12.4 Hz, J=8.5 Hz, 1H), 1.98 (dd, J=12.4 Hz, J=7.4 Hz, 1H), 2.60 (dd, J=14.5 Hz, J=9.0 Hz, 1H), 20 3.07 (dd, J=14.5 Hz, J=5.5 Hz, 1H), 3.36-3.41 (m, 1H), 6.54 (s, 2H), 6.79 (s, 1H), 7.65 (s, 1H)

3-(1H-Imidazol-4-ylmethyl)-1,1-dimethylindan-5-ol

¹H NMR (as HCl-salt, MeOH-d₄): 1.14 (s, 3H), 1.29 (s, 3H), 1.59 (dd, J=12.5 Hz, J=8.8 Hz, 1H), 2.06 (dd, J=12.5 Hz, J=7.5 Hz, 1H), 2.80 (dd, J=15.1 Hz, J=9.3 Hz, 1H), 3.27 (dd, J=15.1 Hz, J=5.2 Hz, 1H), 3.45-3.55 (m, 1H), 6.56 (d, J=2.0 Hz, 1H), 6.65 (dd, J=8.1 Hz, J=2.0 Hz, 1H), 6.96 (d, J=8.1 Hz, 1H), 7.32 (s, 1H), 8.83 (s, 1H)

3 0 EXAMPLE 16**4-(1,2,3,4-Tetrahydronaphthalen-1-ylmethyl)-1H-imidazole**

The procedure of Example 12 is repeated except that 1-tetralone is used in place of 1-indanone. The melting point of the hydrochloride salt is 185-188 °C.

¹H NMR (as HCl-salt, MeOH-d₄): 1.59-1.93 (m, 4H), 2.70-2.80 (m, 2H), 2.96 (dd, J=14.8 Hz, J=9.5 Hz, 1H), 3.08-3.22 (m, 2H), 7.08-7.14 (m, 4H), 7.25 (s, 1H), 8.81 (s, 1H)

Using the same method the following compounds were prepared:

- 4-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-1H-imidazole. M.p. of hydrochloride 210-218 °C.
1H NMR (as HCl-salt, MeOH-d4): 1.58-1.64 (m, 1H), 1.71-1.86 (m, 3H), 2.50-2.60 (m, 1H), 2.66-2.74 (m, 1H), 2.96 (dd, J=14.8 Hz, J=9.5 Hz, 1H), 3.05-3.18 (m, 2H), 3.79 (s, 3H), 6.73-6.77 (m, 2H), 7.09 (t, 1H), 7.25 (s, 1H), 8.81 (s, 1H)
- 4-(6-Methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-1H-imidazole M.p. of hydrochloride 184-191°C.
1H NMR (as HCl-salt, MeOH-d4): 1.58-1.88 (m, 4H), 2.70-2.76 (m, 2H), 2.93 (dd, J=14.5 Hz, J=9.2 Hz, 1H), 3.04-3.32 (m, 2H), 3.74 (s, 3H), 6.63 (d, J=2.5 Hz, 1H), 6.69 (dd, 8.4 Hz, J=2.5 Hz, 1H), 7.03 (d, J=8.4 Hz, 1H), 7.24 (s, 1H), 8.81 (s, 1H)
- 4-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-1H-imidazole. M.p. of hydrochloride 180-183 °C.
1H NMR (as base, CDCl₃): 1.59-1.82 (m, 4H), 2.64-2.68 (m, 2H), 2.85 (dd, J=14.6 Hz, J=9.3 Hz, 1H), 3.01 (dd, J=14.6 Hz, J=4.8 Hz, 1H), 3.12-3.17 (m, 1H), 3.72 (s, 3H), 6.68-6.71 (m, 2H), 6.78 (s, 1H), 6.97-7.00 (m, 1H), 7.56 (s, 1H)
- 4-(4-Methyl-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-1H-imidazole
The product is the mixture of two isomers ad and bc (85 % ad and 15 % bc).
1H NMR (as HCl-salt, MeOH-d4): 1.25 (d, J=7.0 Hz, -CH₃, bc isomer), 1.30 (d, J=7.0 Hz, -CH₃, ad isomer), 1.50-2.10 (m, 4H), 2.80-3.04 (m, 2H), 3.10-3.20 (m, 2H), 7.10-7.26 (m, 5H), 8.83 (s, 1H)
- EXAMPLE 17
- 4-(7-tert-Butyl-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-1H-imidazole
Sulfuric acid (0.75 ml) is added into the mixture of 4-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-1H-imidazole hydrochloride (75 mg) and tert-butanol (3 ml). The mixture is stirred at 35-40 °C for 15 hours. The reaction mixture is poured into water and is made alkaline with sodium hydroxide. The product is extracted into methylene chloride which is washed with water, dried

with sodium sulfate and evaporated to dryness. The residue consisting of crude product is converted to its hydrochloride salt in ethyl acetate. The yield is 40 mg.

5 ^1H NMR (as HCl-salt, MeOH-d₄): 1.28 (s, 9H), 1.65-1.95 (m, 4H), 2.70-2.80 (m, 2H), 2.87-3.10 (m, 3H), 3.78 (s, 3H), 6.63 (s, 1H), 6.79 (s, 1H), 7.22 (s, 1H), 8.81 (s, 1H)

EXAMPLE 18

10 5-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydronaphthalen-2-ol

A stirred mixture of 4-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-1H-imidazole (220 mg) and 48 % hydrobromic acid (11 ml) is heated under reflux for one hour. The cooled reaction mixture is poured into water and is 15 made basic with ammonium hydroxide solution. The product is extracted into ethyl acetate which is washed with water, dried with sodium sulfate and evaporated to dryness. The crude product is converted to its hydrochloride salt in ethyl acetate. The yield is 130 mg, m.p. 200-205°C.
1H NMR (as HCl-salt, MeOH-d₄): 1.54-1.90 (m, 4H), 2.62-2.72 (m, 2H), 2.88-20 3.11 (m, 3H), 6.51 (d, J=2.5 Hz, 1H), 6.56 (dd, J=8.3 Hz, J=2.5 Hz, 1H), 6.94 (d, J=8.3 Hz, 1H), 7.23 (s, 1H), 8.81 (s, 1H)

Using the same method the following compound was prepared:

25 8-(1H-Imidazol-4-ylmethyl)-5,6,7,8-tetrahydronaphthalen-2-ol. M.p. of hydrochloride 245-251 °C.
1H NMR (as HCl-salt. MeOH-d₄): 1.53-1.89 (m, 4H), 2.60-2.70 (m, 2H), 2.90-2.99 (m, 1H), 3.05-3.12 (m, 2H), 6.55-6.60 (m, 2H), 6.90 (d, J=8.0 Hz, 1H), 7.24 (s, 1H), 8.80 (s, 1H)

30 Example 19

6-Bromo-3-(1H-imidazol-4-ylmethyl)-indan-5-ol

35 Bromine (130 mg, 1 eq.) is added dropwise to a stirred suspension of 3-(1H-imidazol-4-ylmethyl)-indan-5-ol hydrochloride (130 mg) in acetic acid (6 ml). The mixture is stirred at 20-23 °C for 3 hours. The reaction mixture is then poured into water and is made alkaline with ammonium hydroxide solution. The product is extracted into ethyl acetate which is washed with water, dried

with sodium sulfate and evaporated to dryness. The product is purified by flash chromatography using methylene chloride-methanol as eluent and is then converted to the hydrochloride salt in ethyl acetate-ethanol solution.

- 5 ^1H NMR (as HCl-salt, MeOH-d4): 1.71-1.83 (m, 1H), 2.18-2.30 (m, 1H), 2.72-
1.89 (m, 3H), 3.10 (dd, J=14.9 Hz, J=5.9 Hz, 1H), 3.36-3.46 (m, 1H), 6.65 (s,
1H), 7.29 (s, 2H), 8.81 (s, 1H)

Example 20

- 10 1,3-Dibromo-8-(1H-imidazol-4-ylmethyl)-5,6,7,8-tetrahydronaphthalen-2-ol

Bromine (190 mg, 2 eq.) is added dropwise to a stirred suspension of 8-(1H-imidazol-4-ylmethyl)-5,6,7,8-tetrahydronaphthalen-2-ol hydrochloride (150 mg) in acetic acid (5 ml). The mixture is stirred at 20-23 °C for 3 hours. The 15 reaction mixture is then poured into water and is made alkaline with ammonium hydroxide solution. The product is extracted into ethyl acetate which is washed with water, dried with sodium sulfate and evaporated to dryness. The product is purified by flash chromatography using methylene chloride-methanol as eluent and is then converted to the hydrochloride salt in 20 ethyl acetate-ethanol solution.
 ^1H NMR (MeOH-d4): 1.51-1.93 (m, 4H), 2.56-2.75 (m, 3H), 2.99 (dd, J=14.8 Hz, J=3.2 Hz, 1H), 3.30-3.33 (m, 1H), 6.88 (s, 1H), 7.23 (s, 1H), 7.61 (s, 1H)

Using the same method the following compounds were prepared:

- 25 4,6-Dibromo-3-(1H-imidazol-4-ylmethyl)-indan-5-ol
 ^1H NMR (MeOH-d4): 1.95-2.16 (m, 2H), 2.58-2.89 (m, 3H), 3.02 (dd, J=14.6 Hz, J=3.5 Hz, 1H), 3.45-3.52 (m, 1H), 6.72 (s, 1H), 7.23 (s, 1H), 7.62 (s, 1H)

30 5,7-Dibromo-1-(1H-imidazol-4-ylmethyl)-indan-4-ol
 ^1H NMR (as HCl-salt, MeOH-d4): 1.93-2.01 (m, 1H), 2.19-2.33 (m, 1H), 2.80-3.07 (m, 3H), 3.12 (dd, J=15.2 Hz, J=4.9 Hz, 1H), 3.51-3.59 (m, 1H), 7.25 (s, 1H), 7.46 (s, 1H), 8.82 (s, 1H)

Example 21**6-Hydroxymethyl-3-(1H-imidazol-4-ylmethyl)-indan-5-ol**

5

a) 1-(1H-Imidazol-4-ylmethyl)-6-methoxyindan-5-carbaldehyde

Tin(IV)chloride (1.60 g) is added dropwise to a stirred solution of dichloromethyl methyl ether (0.68 g) in methylene chloride (12 ml) with ice cooling under a nitrogen atmosphere. The solution is stirred at 0 °C for one hour before adding a solution of 4-(6-methoxyindan-1-ylmethyl)-1H-imidazole (0.60 g) in methylene chloride (4 ml). The resulting mixture is allowed to warm to ambient temperature while being stirred for 4 hours. The mixture is then poured into cold water and is made basic with ammonium hydroxide solution.

10 The product is extracted into methylene chloride which is washed with water, dried with sodium sulfate and evaporated to dryness. The crude product is purified by flash chromatography using methylene chloride-methanol as eluent.

15 ^1H NMR (CDCl_3): 1.78-1.90 (m, 1H), 2.21-2.31 (m, 1H), 2.72-2.86 (m, 3H),

20 3.04 (dd, $J=14.5$ Hz, $J=6.0$ Hz, 1H), 3.50-3.61 (m, 1H), 3.85 (s, 3H), 6.75 (s, 1H), 6.79 (s, 1H), 7.61 (s, 1H), 7.66 (s, 1H), 10.40 (s, 1H)

b) 6-Hydroxy-1-(1H-imidazol-4-ylmethyl)-indan-5-carbaldehyde

25 Boron tribromide 1.0 M solution in methylene chloride (2 ml) is added dropwise to a stirred solution of 1-(1H-imidazol-4-ylmethyl)-6-methoxyindan-5-carbaldehyde (144 mg) in methylene chloride (10 ml) at -70 °C under a nitrogen atmosphere. After the addition the mixture is allowed to warm to room temperature and is stirred for 3 hours. The mixture is then poured into cold water and is made basic with ammonium hydroxide solution. The product is extracted into methylene chloride which is washed with water, dried with sodium sulfate and evaporated to dryness. The crude product is purified by flash chromatography using methylene chloride - methanol as eluent and crystallized from ethyl acetate.

30 35 ^1H NMR (CDCl_3): 1.76-1.88 (m, 1H), 2.20-2.32 (m, 1H), 2.71-2.91 (m, 3H), 3.02 (dd, $J=14.7$ Hz, $J=5.9$ Hz, 1H), 3.44-3.54 (m, 1H), 6.73 (s, 1H), 6.76 (s, 1H), 7.36 (s, 1H), 7.54 (s, 1H), 9.81 (s, 1H)

c) 6-Hydroxymethyl-3-(1H-imidazol-4-ylmethyl)-indan-5-ol

Sodium borohydride (8 mg) is added into a solution of 6-hydroxy-1-(1H-imidazol-4-ylmethyl)-indan-5-carbaldehyde (44 mg) in ethanol (6 ml). The mixture is stirred at room temperature for one hour and then poured into water. The product is extracted into ethyl acetate which is washed with water, dried with sodium sulfate and evaporated to dryness. The crude product is purified by flash chromatography using methylene chloride-methanol as eluent and crystallized from ethyl acetate.

1 H NMR ($\text{CDCl}_3 + \text{MeOH-d}_4$): 1.66-1.77 (m, 1H), 2.12-2.23 (m, 1H), 2.62-2.81 (m, 3H), 2.93 (dd, $J=14.7$ Hz, $J=5.7$ Hz, 1H), 3.30-3.40 (m, 1H), 4.68 (s, 2H), 6.58 (s, 1H), 6.70 (s, 1H), 6.97 (s, 1H), 7.49 (s, 1H)

Example 22

15 6-Hydroxymethyl-1-(1H-imidazol-4-ylmethyl)-indan-5-ol

a) 3-(1H-Imidazol-4-ylmethyl)-6-methoxyindan-5-carbaldehyde

20 Tin(IV)chloride (800 mg) is added dropwise to a stirred solution of dichloromethyl methyl ether (343 mg) in methylene chloride (8 ml) with ice cooling under a nitrogen atmosphere. The solution is stirred at 0 °C for one hour before adding a solution of 4-(5-methoxyindan-1-ylmethyl)-1H-imidazole (300 mg) in methylene chloride (4 ml). The resulting mixture is allowed to 25 warm to ambient temperature while being stirred for 4 hours. The mixture is then poured into cold water and is made basic with ammonium hydroxide solution. Work-up of the mixture gives the crude product which is purified by flash chromatography and recrystallized from ethyl acetate.

1 H NMR (CDCl_3): 1.78-1.90 (m, 1H), 2.22-2.33 (m, 1H), 2.73-2.96 (m, 3H), 3.05 (dd, $J=14.6$ Hz, $J=5.5$ Hz, 1H), 3.43-3.53 (m, 1H), 3.90 (s, 3H), 6.76 (s, 1H), 6.84 (s, 1H), 7.52 (s, 1H), 7.61 (s, 1H), 10.39 (s, 1H)

b) 6-Hydroxy-3-(1H-imidazol-4-ylmethyl)-indan-5-carbaldehyde

35 Boron tribromide 1.0 M solution in methylene chloride (3.9 ml) is added dropwise to a stirred solution of 3-(1H-imidazol-4-ylmethyl)-6-methoxyindan-5-carbaldehyde (318 mg) in methylene chloride (15 ml) at -70 °C under a nitrogen atmosphere. After the addition the mixture is allowed to warm to room temperature and is stirred for 3 hours. The mixture is then poured into cold

water and is made basic with ammonium hydroxide solution. Work-up of the mixture gives the crude product which is purified by flash chromatography and recrystallized from ethyl acetate.

- 5 ^1H NMR (CDCl_3): 1.77-1.89 (m, 1H), 2.22-2.34 (m, 1H), 2.75-2.90 (m, 3H),
 3.01 (dd, $J=14.6$ Hz, $J=6.2$ Hz, 1H), 3.47-3.56 (m, 1H), 6.77 (s, 1H), 6.83 (s, 1H), 7.20 (s, 1H), 7.61 (s, 1H), 9.76 (s, 1H)

c) 6-Hydroxymethyl-1-(1H-imidazol-4-ylmethyl)-indan-5-ol

- 10 Sodium borohydride (10 mg) is added into a solution of 6-hydroxy-3-(1H-imidazol-4-ylmethyl)-indan-5-carbaldehyde (58 mg) in ethanol (10 ml). The mixture is stirred at room temperature for one hour and then poured into water. Work-up of the mixture gives the crude product which is purified by flash chromatography and recrystallized from ethyl acetate.
- 15 ^1H NMR (MeOH-d_4): 1.62-1.72 (m, 1H), 2.08-2.19 (m, 1H), 2.59-2.76 (m, 3H), 2.99 (dd, $J=14.4$ Hz, $J=5.2$ Hz, 1H), 3.28-3.38 (m, 1H), 4.59 (s, 2H), 6.62 (s, 1H), 6.73 (s, 1H), 7.01 (s, 1H), 7.58 (s, 1H)

EXAMPLE 23

20

3-[1-(1H-Imidazol-4-yl)-propyl]-indan-5-ol

a) 4-[1-(6-Methoxyindan-1-yl)-propyl]-1H-imidazole

- 25 The procedure of Example 12 is repeated except that 1-(3-benzyl-3H-imidazol-4-yl)-propan-1-one is used in place of 3-benzyl-3H-imidazole-4-carbaldehyde and 6-methoxyindan-1-one is used in place of 1-indanone. The product is a mixture of two diastereomers (1:1).

- 30 ^1H NMR (as HCl-salt, MeOH-d_4): 0.86 (t, 3H), 0.92 (t, 3H), 1.65-1.95 (m, 4H), 1.98-2.08 (m, 2H), 2.15-2.25 (m, 2H), 2.50-2.73 (m, 4H), 2.96-3.04 (m, 1H), 3.10-3.18 (m, 1H), 3.35-3.50 (m, 2H), 3.69 (s, 3H), 3.78 (s, 3H), 6.38 (d, $J=2.3$ Hz, 1H), 6.68-6.73 (m, 2H), 6.85 (d, $J=2.3$ Hz, 1H), 7.03 (d, $J=8.2$ Hz, 1H), 7.06 (d, $J=8.2$ Hz, 1H), 7.23 (s, 1H), 7.28 (s, 1H), 8.74 (s, 1H), 8.85 (s, 1H)

- 35 b) 3-[1-(1H-Imidazol-4-yl)-propyl]-indan-5-ol

A stirred mixture of 4-[1-(6-methoxyindan-1-yl)-propyl]-1H-imidazole (174 mg) and 48 % hydrobromic acid (9 ml) is heated under reflux for 50 minutes. The cooled reaction mixture is poured into water and is made basic with

ammonium hydroxide solution. The product is extracted into ethyl acetate which is washed with water, dried with sodium sulfate and evaporated to dryness. The crude product is purified by flash chromatography using methylene chloride- methanol as eluent. The product is a mixture of two

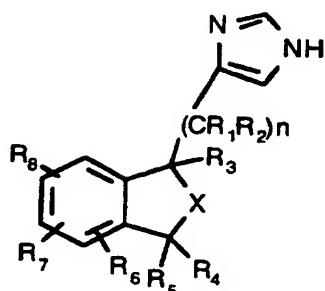
5 diastereomers (1:1).

¹H NMR (MeOH-d₄): 0.79 (t, 3H), 0.84 (t, 3H), 1.60-2.14 (m, 8H), 2.51-2.63 (m, 4H), 2.78-2.85 (m, 2H), 3.27-3.38 (m, 2H), 6.31 (d, J=2.2 Hz, 1H), 6.51-6.55 (m, 2H), 6.59 (s, 1H), 6.64 (s, 1H), 6.68 (d, J=2.2 Hz, 1H), 6.89 (d, J=8.5 Hz, 1H), 6.92 (d, J=8.5 Hz, 1H), 7.52 (s, 1H), 7.59 (s, 1H)

CLAIMS

1. An imidazole derivative which is a compound of formula I

5

**n** is 0 or 1**R1** is hydrogen or C1-C4-alkyl10 **R2** is hydrogen or **R2** and **R3** together form a double bond**R3** is hydrogen or C1-C4-alkyl or **R2** and **R3** together form a double bond**R4** is hydrogen, C1-C4-alkyl, hydroxy or C1-C4-alkoxy**R5** is hydrogen or C1-C4-alkyl or **R4** and **R5** together with the carbon atom to which they are attached form a carbonyl group15 **R6**, **R7** and **R8** are each the same or different and are independently hydrogen, C1-C4-alkyl or C2-C4-alkenyl, C3-C7-cycloalkyl, hydroxy, C1-C4-alkoxy, C1-C4-hydroxyalkyl, thiol, C1-4-alkylthio, C1-4-alkylthiol, halogen, trifluoromethyl, nitro or optionally substituted amino**X** is -CHR9-(CHR10)m-20 **m** is 0 or 1and **R9** and **R10** are each the same or different and are independently hydrogen or C1-C4-alkyl;

or a pharmaceutically acceptable ester or salt thereof.

2. A derivative according to claim 1, wherein **n=m=0**.

25

3. A derivative according to claim 1 or 2, wherein **R6**, **R7** and **R8** are each hydrogen.30 4. A derivative according to claim 1 or 2, wherein **R6** is C1-C4-alkyl at the position 4 or 6 of the indane ring and **R7** and **R8** are hydrogen.

5. A derivative according to claim 1 or 2, wherein R₆ is C₁-C₄-alkoxy at the position 7 of the indane ring and R₇ and R₈ are hydrogen.

6. A derivative according to claim 1, wherein n=0 and m=1 and R₃ to R₁₀ 5 are all hydrogen.

7. A derivative according to claim 1, wherein n=1 and m=0.

8. A derivative according to claim 7, wherein R₁ is methyl or ethyl.

10 9. A derivative according to claim 7 or 8, wherein R₆, R₇ and R₈ are each hydrogen.

15 10. A derivative according to claim 7 or 8, wherein R₆ is hydroxy at the position 4 or 6 of the indane ring and R₇ and R₈ are hydrogen.

11. A derivative according to claim 7 or 8, wherein R₆ is hydroxy at the position 5 of the indane ring and R₇ is hydroxy or C₁-C₄-alkyl or C₁-C₄-hydroxyalkyl at the position 6 of the indane ring and R₈ is hydrogen.

20 12. A derivative according to claim 1, wherein n=m=1.

13. A derivative according to claim 12, wherein R₅ to R₈ are all hydrogen.

25 14. A derivative according to claim 12, wherein R₆ is a hydroxy group at the position 7 of the 1,2,3,4-tetrahydronaphthyl ring and R₇ and R₈ are hydrogen.

30 15. Use of a derivative as defined in any one of claims 1 to 14 as a medicament.

16. A pharmaceutically acceptable composition comprising a derivative as defined in any one of claims 1 to 14 and a pharmaceutically acceptable carrier.

35 17. A derivative as defined in any one of claims 1 to 14, for use in a method of treatment of the human or animal body.

18. A derivative as defined in any one of claims 1 to 14, for use in the treatment of hypertension, glaucoma, chronic and acute pain, migraine, diarrhea, common cold, ischemia, addiction to chemical substances, anxiety, especially preoperative anxiety and different neurological, musculoskeletal, psychiatric and cognition disorders or as an adjunct to anesthesia.
19. Use of a derivative as defined in any of the claims 1 to 14 in the manufacture of a medicament for use in the treatment of hypertension, glaucoma, chronic and acute pain, migraine, diarrhea, common cold, ischemia, addiction to chemical substances, anxiety, especially preoperative anxiety and different neurological, musculoskeletal, psychiatric and cognition disorders.
20. Use of a derivative as defined in any one of claims 1 to 14 in the manufacture of a medicament for use as an adjunct to anesthesia.
21. A method for the treatment of hypertension, glaucoma, chronic and pain, migraine, diarrhea, common cold, ischemia, addiction to chemical substances, anxiety, especially preoperative anxiety and different neurological, musculoskeletal, psychiatric and cognition disorders by administering to a subject in need of such treatment an effective amount of a derivative as defined in any one of claims 1 to 14.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FI 96/00518

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D233/54 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 0 717 037 A (UCB SA) 19 June 1996	1-6, 15-21
X	see the whole document see page 2, line 7 - line 10 ---	1,3,6
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 15, 22 July 1994, WASHINGTON US, pages 2328-2333, XP002022576 S.-S. HONG ET AL.: "A Structure-Activity Relationship Study of Benzylic Modifications of 4-[1-(1-Naphthyl)ethyl]-1H-imidazoles on alpha1- and alpha2-Adrenergic Receptors" see the whole document; in particular: page 2330, table 1, compound 2 ---	1,3,12, 13,15-21
	-/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

1

Date of the actual completion of the international search

13 January 1997

Date of mailing of the international search report

22.01.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl.
Fax (+ 31-70) 340-3016

Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

Inte	nal Application No
PCT/FI 96/00518	

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 183 492 A (FARMOS OY) 4 June 1986 see page 1, line 5 - line 20 -----	1-6, 15-21

INTERNATIONAL SEARCH REPORT

International application No.

PCI/FI 96/00518

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 21 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte: nal Application No

PCT/FI 96/00518

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0717037	19-06-96	AU-A- 4036895 BG-A- 100208 CA-A- 2165133 CZ-A- 9503271 FI-A- 955927 JP-A- 8208622 NO-A- 955034 NZ-A- 280646 PL-A- 311736 ZA-A- 9510554	20-06-96 31-07-96 15-06-96 17-07-96 15-06-96 13-08-96 17-06-96 27-08-96 24-06-96 13-06-96
EP-A-0183492	04-06-86	GB-A- 2167408 AU-A- 3332989 AU-B- 586839 AU-A- 5008385 BG-B- 60762 CA-A,C 1266669 DE-A- 3587045 EP-A- 0310745 HK-A- 3592 IE-B- 58165 JP-B- 6004597 JP-A- 61143366 SU-A- 1424736 US-A- 4689339	29-05-86 10-08-89 27-07-89 29-05-86 29-02-96 13-03-90 11-03-93 12-04-89 17-01-92 28-07-93 19-01-94 01-07-86 15-09-88 25-08-87

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

This Page Blank (uspto)